

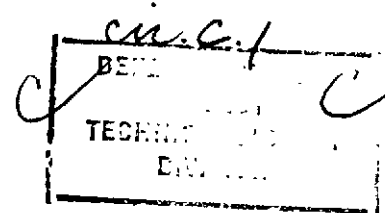
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# INITIAL HUMAN RESPONSE TO NUCLEAR RADIATION

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Technical Report

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This report documents the results of the first phase of an investigation into the nuclear effects on military troop performance. Both signs and symptoms associated with radiation sickness were examined to develop models of human response to radiation as a function of dose, time and symptom severity. Data on the early symptomatic effects of radiation exposure were gathered from some 150 books, articles and monographs. The analysis of this data focused on human data collected from the victims of nuclear accidents and		

## 20. ABSTRACT (continued)

therapy patients. Data from the survivors of the Japanese atomic bombs were excluded because of data imprecision and questions raised about the accuracy of reported exposure levels. A hypothetical exposed population was divided into response groups based on the sensitivity of individuals to radiation: hyper-, hypo-, and normsensitives. The population was also classified by the severity of their symptoms; unaffected and mildly, moderately and severely affected. Using this data, relationships for the onset time and duration of acute symptoms after a given radiation dose were developed.

Conceptual models were then derived for (1) individual response as a function of dose, time after exposure, and severity of symptoms, (2) population response (percentage affected in various degrees), and (3) links between individual and population responses. To develop these models further for the second phase, a better understanding of the relation between acute radiation exposure and subsequent illness as a function of time as well as more data from noninvasive studies of therapy patients is needed. Once the connection between radiation exposure and sickness is sufficiently well understood, it should be possible to make more definitive statements about how human performance will be affected by radiation.

## SUMMARY

According to U.S. Army criteria for the employment of combat units after a nuclear attack, a radiation dose of at least 3000 rads free-in-air is required to render troops incapable of combat performance. Current scenarios suggest that for every soldier who receives an incapacitating radiation dose, another will receive a lethal but not incapacitating dose, say, 400 to 3000 rads. Two more soldiers will receive doses between "troop safety" and lethal levels (50 to 400 rads). Many will show symptoms of radiation sickness and impaired ability to perform their normal combat tasks. The effectiveness of units manned by such sick and "walking dead" troops could become an important factor in the battlefield employment of nuclear weapons. With the continuing possibility that such weapons might be used, it is troubling that radiation-induced effects on combat performance remain poorly understood.

We have undertaken a two-phase research program to improve our understanding of the effects of ionizing radiation at the "intermediate" dose range referred to above. The virtual absence of empirical data directly relating radiation exposure to human performance--much less performance in combat--necessitates an indirect approach. In the first research phase, reported here, we examined the signs and symptoms associated with radiation sickness to develop models of human response to radiation as a function of dose, time, and symptom severity. In the second phase, we plan to extend the response models to estimate how various symptoms impair physical and mental performance and, in turn, alter combat unit effectiveness.

From some 150 selected books, articles, and monographs, we gathered data on the early symptomatic effects of radiation exposure. For the analysis we focused on human data collected from the victims of nuclear accidents and therapy patients. We excluded data from animal experiments because of the tenuousness of the link between animal and human performance after irradiation. We also excluded data from the survivors of the Japanese atomic bombs because of data imprecision and the serious

questions that have been raised about the accuracy of reported exposure levels.

We divided a hypothetical exposed population into response groups based on the sensitivity of individuals to radiation: hyper-, hypo-, and normosensitives. We also classified such a population by the severity of their symptoms: unaffected and mildly, moderately, and severely affected.

Using the data, we developed relationships for the onset time and duration of acute symptoms after a given radiation dose. We then derived conceptual models for (1) individual response as a function of dose, time after exposure, and severity of symptoms, (2) population response (percentage affected in various degrees), and (3) links between individual and population responses.

To develop the models further for the second phase of this research, we need a much better understanding of the relation between acute radiation exposure and subsequent illness as a function of time. We need more data from noninvasive studies of therapy patients. Any new data on nuclear accidents should be carefully studied. It may be possible to make better use of data on irradiated animals, and to clarify the relation of animal behavior after irradiation to human behavior under similar conditions. Reexamination of the data on Japanese atomic bomb survivors may be worthwhile; the questionnaires they completed contain much detail.

Once the connection between radiation exposure and sickness is sufficiently well understood, it should be possible to make more definitive statements about how human performance will be affected by radiation. The role of such factors as psychological state, age, and training should also be considered. A study of specific military tasks and analysis of the human effort required will help correlate radiation sickness with combat performance.

Even when performance impairment is correlated with radiation exposure for *individuals*, however, questions will remain about the effectiveness of *units* in accomplishing their combat missions. To

investigate the influence of individual performance impairment on unit effectiveness, any of several computerized models of military unit performance could be adapted to simulate the incapacitation effects of nuclear radiation. Models of small units (tank crews, artillery batteries, and the like) are needed for evaluating the speed, accuracy, and endurance with which crew members perform their assigned tasks. Then, links can be made to the activities of larger units such as battalions, divisions, and regiments.

## PREFACE

This note reports on the first phase of an investigation of nuclear radiation effects on military troop performance for the Defense Nuclear Agency (DNA). In this phase, data were gathered and concepts developed for models of human symptomatic response to radiation. In the second phase, the models will be used to infer performance effects.

DNA staff members Cyrus Knowles and David Auton guided this effort. H. Rodney Withers of the Department of Radiation Oncology, Center for Health Sciences, University of California at Los Angeles, served as a consultant on radiobiological effects and wrote Appendix B.



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## SECTION 1

### INTRODUCTION

According to U.S. Army criteria for the employment of combat units after a nuclear attack, a radiation dose of at least 3000 rads free-in-air is required to render troops incapable of combat performance. Current scenarios suggest that for every soldier who receives an incapacitating radiation dose, another will receive a lethal but not incapacitating dose, say, 400 to 3000 rads. Two more soldiers will receive doses between "troop safety" and lethal levels (50 to 400 rads). Many will show symptoms of radiation sickness and impaired ability to perform their normal combat tasks. The effectiveness of units manned by such sick and "walking dead" troops could become an important factor in the battlefield employment of nuclear weapons. With the continuing possibility that such weapons might be used, it is troubling that radiation-induced effects on combat performance remain poorly understood.

This is an initial report on research intended to improve our ability to predict the degree of functional impairment in military units exposed to ionizing radiation.

For application to battlefield operations, we are concerned with early radiation effects, those occurring within a few weeks of exposure; because the effects of intermediate radiation doses are least well understood, we are mainly concerned with exposure levels of 100 to 3000 rads free-in-air.

There are no data pertaining directly to the effects of single doses of radiation on combat performance; and studies of general performance effects have yielded inconclusive results. Wolfgang and Maier [1972] found no performance impairment in relatively young, healthy adults receiving irradiation to the spinal cord or brain. However, the exposures occurred over 3 to 4 weeks and covered only small portions of the body. Payne [1963], Saenger et al. [1968], and Gottschalk et al. [1969] found it impossible to determine whether therapeutic irradiation in total-body and partial-body doses impaired psychomotor or cognitive

performance. The only data available for those studies, however, pertained to older, terminal cancer patients; the analyses did not control for age, education, motivation, or intelligence, so the effects of those variables could not be separated from radiation effects. In addition, the total-body doses were low for consideration of incapacitating effects (~10 to ~200 rads).

More recently, Saenger et al. [1971] suggest that cognitive dysfunction increases immediately after irradiation. Vodopick and Andrews [1980] studied radiation effects in a 32-year-old victim exposed to 127 rads in a nuclear laboratory accident. They found excessive fatigability in the victim soon after exposure, which they conjecture was due to muscle damage and cell destruction.

Given the lack of empirical data relating combat effectiveness to radiation exposure levels, a reasonable approach would be to examine the symptoms<sup>\*</sup> associated with radiation sickness and infer from them the effects on performance. Figure 1 suggests the routes by which such inferences could be made, showing the directness of various relationships impinging on human performance after exposure to ionizing radiation. The solid arrows indicate established relationships; the broken arrows, presumed relationships to be confirmed by empirical data; the arrows containing diamonds, relationships that must be made by inference. Thus, data collected from victims of nuclear accidents, therapy patients, and Japanese atom bomb survivors could be used directly to determine what radiation doses produce what symptoms. For animals, the data allow going further and determining what doses produce what performance effects; for humans, however, those effects must be inferred. Figure 1 also shows that data on nonradiation insults producing symptoms similar to those of radiation sickness might be used to infer performance effects. Morgan and Alluisi [1978] made such inferences in controlled studies of tularemia and sand fly fever victims.

Following two of the routes shown in Fig. 1, we have pursued this research in two phases, depicted in Fig. 2. In the first phase, reported

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<sup>\*</sup>Throughout this report, "symptoms" is used to mean both subjective evidence and objective signs of radiation sickness.

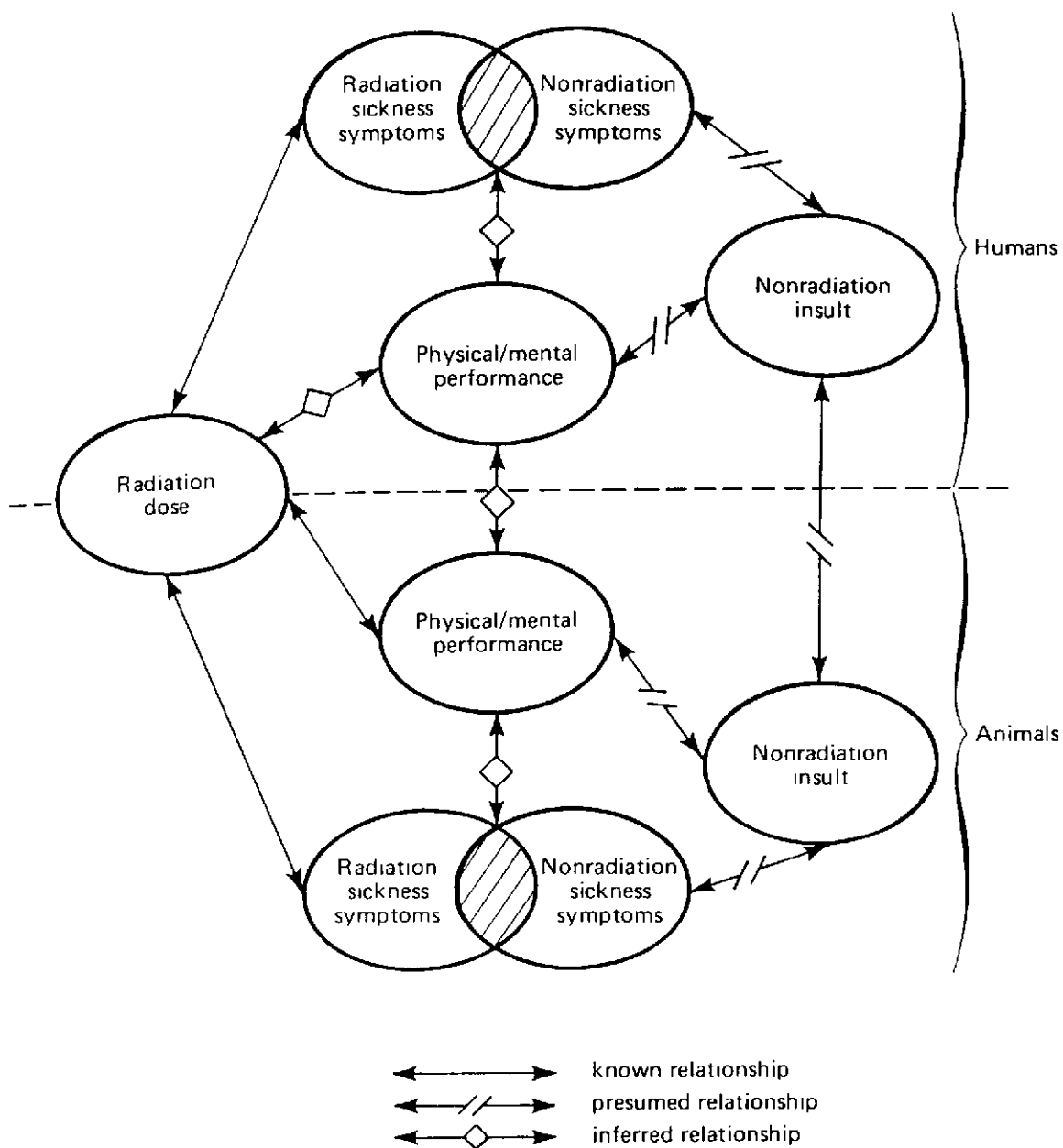


Figure 1. Ways of investigating the effects of ionizing radiation on human performance.

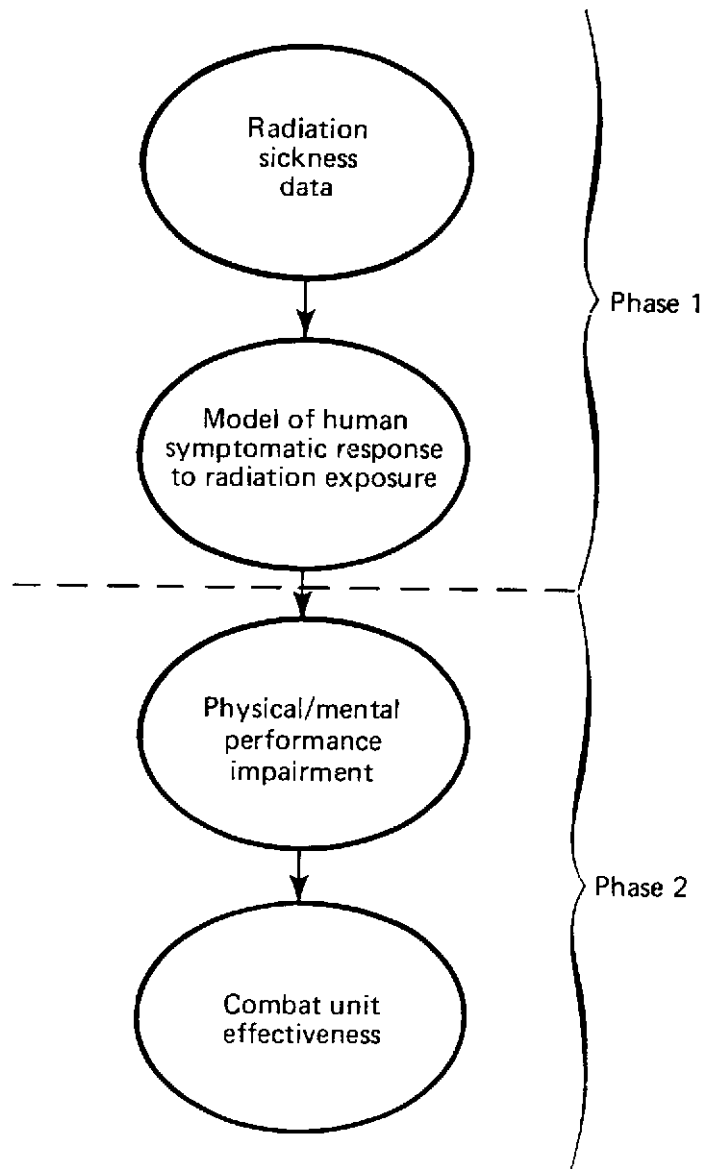


Figure 2. Research plan.

here, we gathered and analyzed radiation sickness data (primarily from accident and therapy cases<sup>\*</sup>) to develop a model of human symptomatic response to radiation as a function of time following a given dose. In the second phase, we will extend the response model to estimate how various symptoms impair physical and mental performance and, in turn, affect combat unit effectiveness.<sup>†</sup>

Section 2 describes the data sources we used and the symptomatic information we drew from them. Using that information, Sec. 3 classifies a hypothetical affected population into response groups and develops models of how each might respond to radiation as a function of dose and time after exposure. Section 4 presents our conclusions and recommendations.

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<sup>\*</sup>Data on Japanese atom bomb victims were gathered but later excluded from the response model. Dispute has arisen over the exposure levels associated with the bombings; until it is resolved, our figures linking symptoms with radiation dose would be questionable. Also, a cursory review of the literature showed unexplainable discrepancies in victims' response syndromes. Consideration of the Japanese data is summarized in Appendix A. We excluded animal experiment data from the present model because of the tenuousness of the link between animal radiation sickness and human performance.

<sup>†</sup>Brode [1977] suggested this research approach and identified much of the data on which this report is based.



## SECTION 2

### SYMPTOMATIC DATA

From a literature search, we assembled some 150 books, articles, and monographs on the early symptomatic effects of radiation exposure. This section describes the resulting data base and the information we extracted from it.

#### SOURCES

We began with the 100 documents used in prior research, including McDonald et al.'s comprehensive study [1976]. They contained information on the following topics:

- Accidents. Data on victims of nuclear accidents.
- Therapy. Data on cancer patients receiving primarily total-body irradiation (TBI).
- Japanese experience. Data on survivors of the atomic bombings in Hiroshima and Nagasaki.
- Composite data and expert opinion. Analyses by physicians and radiobiological specialists drawing on firsthand experience or information in several of the topics listed here.
- Performance impairment in animals. Data from laboratory experiments with animals to determine impairments as a function of radiation dose.
- Performance impairment in humans. Information on persons who were exposed to radiation or who suffered nonradiation insults producing symptoms similar to radiation sickness.
- Drug treatment. Data on the effectiveness of various drugs used to suppress radiation sickness symptoms.
- Military operations. Theoretical considerations of the impact of radiation sickness on the battlefield.
- Background. Miscellaneous information on the effects of exposure to radiation.

We then updated the bibliography with 50 additional documents, primarily on clinically observed human reactions to radiation exposure.\* Each document was assigned to one of the nine topical categories listed above.

#### INFORMATION EXTRACTED

Data in the first four topical categories offered the best potential yield of information on human radiation sickness symptoms as related to dose and postexposure time. After review of the Japanese data, however, we excluded that category from present consideration because the data posed too many problems of interpretation (see Appendix A).

From each document in the remaining categories--nuclear accidents, radiation therapy, composite data, and expert opinion--we extracted data on the following:

- Dose.
- Initial postexposure period: time of exposure, onset time of prodromal symptoms, their nature and duration.
- Latent or remission period: duration and patient's condition.
- Manifest-illness period: time of onset and symptoms, duration, result (recovery or death).

In the remainder of this section we indicate the most useful sources and summarize the information drawn from them.

#### Accidents

A frequent problem with accident data is the uncertainty of the dose to which the victim was actually exposed and its nonuniform

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\*The following sources were consulted: NTIS, Excerpta Medica, Index Medicus, MEDLARS/MEDLINE, DTIC, and BIOSIS data bases; National Academy of Sciences, for summaries of data on Japanese atom bomb victims; Oak Ridge National Laboratory, for results of dosimetry studies on Japanese victims; World Health Organization; National Council of Radiation Protection; Department of Radiation Oncology, UCLA Center for Health Sciences; National Institutes of Health and National Library of Medicine; Armed Forces Radiobiological Research Institute; and U.S. Air Force School of Aerospace Medicine.

distribution in the victim's body. The literature describes many attempts to reconstruct an accident to determine the exposure level more accurately. Another problem is that accident descriptions often lack precise quantitative data. For example, rather than identifying the exact onset time of symptoms, many accounts use phrases like "within the first hour" or "after several minutes." The data cover a wide range of doses (130 to 8800 rads) but, because relatively few accidents have occurred, are sparse over that range. A major uncertainty in interpreting the data is the impact of medical treatment on the symptoms and course of the illness.

Herbert Fanger and Clarence C. Lushbaugh, "Radiation Death from Cardiovascular Shock Following a Criticality Accident," *Archives of Pathology*, Vol. 83, May 1967, pp. 446-460.

Joseph S. Karas and John B. Stanbury, "Fatal Radiation Syndrome from an Accidental Nuclear Excursion," *New England Journal of Medicine*, Vol. 272, No. 15, 15 April 1965, pp. 755-761.

On 24 July 1964, at a United Nuclear Corporation plant in Wood River Junction, Rhode Island, a 38-year-old employee was exposed to 8800 rads. Five to ten minutes after the accident the victim developed severe abdominal pains accompanied by nausea, vomiting, and diarrhea. Recurring episodes of vomiting and diarrhea persisted for about 4 hr. The victim died 49 hr after the accident.

J. W. Howland et al., "The Lockport Incident: Accidental Partial Body Exposure of Humans to Large Doses of X-Radiation," in International Atomic Energy Agency and World Health Organization, *Diagnosis and Treatment of Acute Radiation Injury*, proceedings of a conference held in Geneva, Switzerland, 17-21 October 1960, International Documents Service, New York, 1961.

On 8 March 1960, at a military installation in Lockport, New York, nine employees were exposed to ionizing radiation from an unshielded klystron tube. The dose absorbed by persons not moving much during the exposure period of 20 to 30 min was estimated at 1200 to 1500 rads. The victims were exposed from head to mid-thigh.

Nausea and vomiting began about 30 min after exposure; severe headaches persisted for several hours. Vomiting continued throughout

the first day; nausea and fatigue persisted for a week after exposure and sporadically thereafter for several weeks. The victims experienced lassitude and fatigability over the entire 210-day period of observation.

Michael V. Gilberti, "The 1967 Radiation Accident near Pittsburgh, Pennsylvania, and a Follow-up Report," in K. F. Hubner and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, Inc., New York; 1980.

On 4 October 1967, three technicians, all men, were exposed to whole-body radiation from a linear accelerator. Victim A, age 31, received a dose of 100 rads; victim B, age 29, 300 rads; and victim C, age 40, 600 rads. Victim C also sustained an exposure of 5900 rads to his hands and 2700 rads to his feet.

Victim A showed few clinical symptoms; victim B became nauseated and started to vomit within 1 hr after the accident; victim C experienced nausea, vomiting, and generalized muscle aches 45 min after the accident.

Victim A's hemopoietic condition changed very little and returned to normal much sooner than did that of the other two men, who experienced considerable hemopoietic injury.

H. Jammet et al., "Clinical and Biological Comparison of Two Acute Accidental Irradiations: Mol (1965) and Brescia (1975)," in K. F. Hubner and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, Inc., New York, 1980.

In Mol, Belgium, on 30 December 1965, one person was exposed to 550 rads in a criticality accident with an experimental reactor. Nausea and vomiting began 2 hr after the accident and persisted a few hours. Manifest illness, marked by various infections, showed up 3 weeks later. After 6 weeks, the victim began to recover.

In Brescia, Italy, on 13 May 1975, one person sustained an exposure to 1200 rads from a cobalt 60 source. Nausea and vomiting began 30 min after the accident and persisted a few hours. Manifest illness was apparent 4 days after the accident, and the victim died 3 days later.

H. Vodopick and G. A. Andrews, "The University of Tennessee Comparative Animal Research Laboratory Accident in 1971," in K. F. Hubner and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, Inc., New York, 1980.

On 4 February 1971, a 32-year-old research technologist at the University of Tennessee Comparative Animal Research Laboratory was exposed to a cobalt 60 source for about 40 sec. The estimated midline dose was 127 rads; for the right hand, 1200 rads. Episodes of sudden vomiting not preceded by nausea began 2 hr and 15 min after exposure and recurred 10 times during the next 24 hr. Diarrhea and fever were not present.

During the period of maximum hematological depression, days 24 to 34, the patient remained well. On day 36 a mouth infection was treated with orally administered penicillin. By day 48, all blood counts had returned to normal. Soon after the accident and for 4 months thereafter, the patient experienced great fatigue at the least exertion. The patient returned to work 11 weeks after the accident.

B. Pendic, "The Zero-Energy Reactor Accident at Vinca," in International Atomic Energy Agency and World Health Organization, *Diagnosis and Treatment of Acute Radiation Injury*, proceedings of a conference held in Geneva, Switzerland, 17-21 October 1960, International Documents Service, New York, 1961.

Clarence C. Lushbaugh, "Reflections on Some Recent Progress in Human Radiobiology," *Advances in Radiation Biology*, Vol. 3, Academic Press, New York, 1969.

On 15 October 1958, a zero-energy reactor in Vinca, Yugoslavia, became supercritical and six persons were exposed to radiation. Pendic's 1961 estimate of the dose equivalent (350 to 640 rems) was later revised to 145 to 305 rems by a team of health physicists at Oak Ridge National Laboratory.

Severe nausea and intractable vomiting began in the first hour for those who received higher doses (293 to 305 rems), and in the second hour for those receiving lower doses (226 to 290 rems). The person who absorbed 145 rems became slightly nauseated but did not vomit. Those early reactions were followed by a latent period lasting until the end of the third week. The victims experienced anorexia,

loss of weight, headache, diffuse abdominal pain, weakness, profuse sweating, and insomnia.

During the critical period, weeks 4 through 7, the general condition of the five most heavily irradiated victims deteriorated greatly. Their temperatures rose and infections took hold. They experienced marked nausea followed by abdominal pain, completely lost their appetite, and developed profuse night sweating. With treatment, four of the victims gradually improved from week 7 on, although true convalescence did not begin until the third month. The most heavily irradiated victim died on day 32. The least-irradiated victim recovered more slowly than the others.

Herbert Fanger and Clarence C. Lushbaugh, "Radiation Death from Cardiovascular Shock Following a Criticality Accident," *Archives of Pathology*, Vol. 83, May 1967, pp. 446-460.

On 30 December 1958, during a routine plutonium salvage operation at Los Alamos Scientific Laboratory, a worker received a lethal dose of 4500 rads (original estimate, 9200 rads). The onset of symptoms occurred within 15 min; death came 35 hr later. The victim manifested no neurologic damage until immediately before his death when he became irrational, his behavior became unmanageable, and he went into convulsions. An autopsy revealed no primary neurologic injury but severe cardiovascular changes, suggesting that early radiation deaths might be caused by cardiovascular shock.

Eugene L. Saenger (ed.), *Medical Aspects of Radiation Accidents*, U.S. Atomic Energy Commission, Washington, D.C., 1963.

From studying the histories of accident victims, the author classifies an exposed population in three groups according to dose absorbed.

200 to 400 rads. Nausea and vomiting begin 1 hr after exposure or soon thereafter. Symptoms reach maximum intensity 6 to 8 hr after exposure and subside within 24 to 48 hr. There follows a latent period lasting 2 to 3 weeks during which victims are asymptomatic except for weakness and fatigue. During the manifest-illness period, which begins between days 18 and 21, the victims exhibit mild to moderate hemopoietic injury. Convalescence begins 60 to 90 days after

exposure, and clinical recovery is complete within 6 months, although weakness may persist.

400 to 600 rads. Nausea and vomiting begin within 1 hr after exposure, reaching maximum intensity within 6 to 8 hr. Victims show weakness, fatigue, conjunctivitis, and sweating. Symptoms persist 24 to 48 hr, diminishing gradually. The ensuing latent period lasts 5 to 14 days. The manifest illness begins between days 12 and 14. Victims show moderate hemopoietic injury and definite gastrointestinal changes. During the fourth week, victims become prostrate, lethargic, and intermittently disoriented. Between days 25 and 40, despite vigorous therapy, death may occur, preceded by profound shock and coma.

600 to 1400 rads. Early after exposure, victims experience diarrhea, ataxia, disorientation, coma, or cardiovascular collapse. Victims may pass into the manifest-illness period with a short latent period of 5 to 8 days. Gastrointestinal symptoms predominate, and sometimes survival is too brief for hematological changes to be observed. Death usually occurs 15 to 30 days after exposure.

#### Therapy

Data on the effects of therapeutic radiation pertain to a narrower dose range (150 to 600 rads) than do the accident data. Specific information on radiation sickness symptoms is also limited because the literature focuses on the patient's ailment and how it is affected rather than on the patient's response to radiation exposure per se.

There are two major uncertainties in interpreting the therapy data. Patients' precarious state of health at the time radiation therapy is begun undoubtedly affects their responses but to an unknown degree. The medical treatment patients receive before and after radiation therapy also affects their symptomatic responses, again to an unknown degree. For our purpose, the usefulness of therapy data is restricted to the exposure time before medical rescue efforts such as bone marrow transplants for leukemia patients undergoing total-body irradiation. Reflecting more recent medical experience, Appendix B presents comments by a radiation oncologist on the side effects of total-body irradiation (maximum dose, 2000 rads) in therapy patients.

W. M. Court Brown, "Symptomatic Disturbance after Single Therapeutic Dose of X-Rays," *British Medical Journal*, 11 April 1953, pp. 802-805.

Fifty patients were given a single therapeutic X-ray dose of about 150 rads. They were primarily afflicted with ankylosing spondylitis or reticulosis, diseases requiring irradiation of a large amount of tissue.

Within 2 hr, 42 of the patients (84 percent) developed symptoms such as fatigue, anorexia, nausea, and vomiting. The symptoms continued for 0.5 to 2.5 hr. Then, symptoms gradually subsided in the least radiation-sensitive; fatigue, nausea, or both intensified for an hour and then subsided in the moderately sensitive; and vomiting persisted for 2 to 3 hr in the most sensitive.

Fatigue appeared to be dissociated from nausea and vomiting. The two sets of symptoms may have separate etiologies.

Lowell S. Miller, Gilbert H. Fletcher, and Herbert B. Gerstner, "Radiobiologic Observations on Cancer Patients Treated with Whole-Body X-Irradiation," *Radiation Research*, Vol. 4, 1958, pp. 150-165.

Thirty cancer patients were treated with total-body X-ray doses of 200 rads. Most developed fatigue, anorexia, nausea, and vomiting within 2 hr; symptoms abated after a few days. The symptoms may have been related to patients' psychological state. Three to four weeks after exposure, the patients manifested reduced bone marrow activity and a tendency toward bleeding and infection. Those symptoms subsided 6 to 8 weeks after exposure.

One patient showed severe nausea, vomiting, and prostration 2 hr after exposure and vomited 5 times during the first 24 hr. Extreme weakness and moderate nausea persisted through the first postirradiation day. Thereafter, recovery was rapid.

H. Rodney Withers, Department of Radiation Oncology, UCLA Center for Health Sciences, private communication, 1981.

Dr. Withers reported recent information from colleagues on the incidence of nausea and vomiting among patients undergoing TBI therapy



for leukemia. All received preirradiation medical preparation. Dose and associated response times are summarized below:

<u>Dose (rads)</u>	<u>Onset of Nausea and Vomiting after Treatment Began</u>
200	2 hr
750 (effective dose for prodromal effects, 500-625), 375 (at 25/min) midline to each side of body, 5 min to turn body	25 min
800 (effective dose, 600-650), 200 (at 14/min) to each of four sides of body	45 min to 1 hr

W. D. Rider and R. Hasselback, "The Symptomatic and Hematological Disturbance Following Total Body Radiation of 300-rad Gamma-Ray Irradiation," lectures presented at McGill University, Montreal, August 1967, in *Guidelines to Radiological Health*, U.S. Public Health Service, Washington, D.C., 1968, pp. 139-144.

Twenty patients were treated with a single 300-rad dose of total-body irradiation. Most patients were children or adolescents suffering from Ewing's tumor of the bone. All were in good general condition, with normal results from peripheral blood and bone marrow studies.

Sudden vomiting began 45 to 60 min after exposure and was not always preceded by nausea. It lasted 15 to 20 min, after which the patients became sleepy. Over the next 6 hr, periods of vomiting alternated with periods of sleep and fatigue, the length of the vomiting periods decreasing while the periods of sleep increased.

Then the patients were asymptomatic until day 25, when they showed some purpura and minor bleeding from the gums. Maximum hemopoietic depression occurred between days 25 and 30. Thereafter, recovery was prompt.

#### Composite

Composite studies consist of analyses, projections, and information on diagnosis and treatment, based on data from several sources, including accident victims, therapy patients, Japanese atom bomb victims,

and extrapolations from animal experiments. The data sources are not always identified precisely, so it is difficult to ensure that these composite studies, and hence our analysis, do not duplicate other data. These studies also tend to be insufficiently specific for our purpose; clinical effects, for example, are grouped in wide dose ranges (e.g., 200 to 600 rads).

*NATO Handbook on the Medical Aspects of NBC Defensive Operations*, U.S. Departments of the Army, Navy, and Air Force, AMED P-6, August 1973.

This handbook projects the acute clinical effects of single high doses of total-body irradiation in young healthy adults. Table 1 summarizes the information.

S. Glasstone and P. J. Dolan, *The Effects of Nuclear Weapons*, U.S. Departments of Defense and Energy, 1977.

The authors discuss the effects of total-body irradiation in human beings, drawing from Japanese, accident, and therapy data, and extrapolating from observations of animals. The information pertaining to doses of up to 200 rads is asserted to be reliable because it is based primarily on therapy data; at higher doses, the sparse human data must be supplemented by extrapolation from animal experiments. Table 2 summarizes the information.

E. Laumets, *Time History of Biological Response to Ionizing Radiation*, U.S. Naval Radiological Defense Laboratory, USNRDL-TR-905, 22 November 1965.

Using accident data (1945 to 1958), therapy patient records, and follow-up studies of Japanese atomic bomb victims, the author plots the general course of human responses to total-body irradiation.

For doses of 200 to 600 rads, nausea and vomiting occur 1 to 2 hr after exposure, peak 8 hr after exposure, and subside in 1 to 2 days. Depending inversely on the dose, there follows a latent period lasting 1 or 2 days to 2 weeks during which the victim is asymptomatic. The period of manifest illness begins several days to 2 or 3 weeks after exposure, culminating about week 4. If death does not occur, recovery

Table 1. Projected acute effects of total-body irradiation in healthy adults.

Item	Dose (rads)					
	Sublethal (0-100)	Low Lethal (100-800)			Supralethal (>800)	
		100-200	200-600	600-800	800-3000	>3000
Initial Response						
Nausea and vomiting (percent of victims)	0-5	5-50	50-100	75-100	100	100
Time of onset after exposure (hr)	--	~3-6	~1-4	~1-2	<1	<1
Duration (hr)	--	<24	<24	<48	<48	~48
Combat effectiveness	100%	>80%	Routine tasks only; no com- bat for 6-20 hr	Simple rou- tine tasks only; in- capacitated >24 hr	Progressive incapacitation following early capacity for intermittent heroic action	
Latent Phase						
Duration (days)	--	>14	7-15	0-7	0-2	0
Secondary Response						
Symptoms	None	Moderate leukopenia	Severe leukopenia, purpura, hemorrhage, infection, epilation (>300 rads)		Diarrhea, fever, disturbed electrolyte balance	Convulsions, tremor, ataxia, lethargy
Time of onset after exposure (days)	--	14 or more	Several to 14	Several to 14	2-3	--
Critical period after exposure	--	None	4-6 weeks	4-6 weeks	5-14 days	1-48 hr
Organ most affected	--	← Hemopoietic system →			Gastro- intestinal tract	Central nervous system
Treatment and Prognosis						
Percentage of victims requiring hospital- ization	0	<10	Up to 90	100	100	100
Length of hospital- ization (days)	--	45-60	60-90	90-120	14	?
Therapy	None	Hematologic surveil- lance	Blood transfusion, anti- biotics, rest		Maintenance of elec- trolyte balance	Supportive treatment
Percentage of vic- tims at risk to die	0	0	0-80	80-100	80-100	90-100
Average time of death after exposure	--	--	← 2 weeks to 2 months →		1-2 weeks	2 days

SOURCE: Adapted from J. J. O'Brien [1973], Table 6-11.

Table 2. Acute clinical effects of total-body irradiation.

Dose (rems)						
Item	Therapeutic (100-1000)				Lethal (>1000)	
	Subclinical (0-100)	Clinical Surveillance, 100-200	Therapy Effective, 200-600	Therapy Promising, 600-1000	Therapy Palliative	
					1000-5000	>5000
Postexposure Response Phases						
Initial:						
Onset postexposure	--	3-6 hr	0.5-6 hr	15-30 min	5-30 min	Almost
Duration	--	≤1 day	1-2 days	≤2 days	≤1 day	immediately <sup>d</sup>
Latent:						
Onset postexposure	--	≤1 day	1-2 days	≤2 days	≤1 day <sup>b</sup>	Almost
Duration	--	≤2 weeks	1-4 weeks	5-10 days	0-7 days <sup>b</sup>	immediately <sup>d</sup>
Final:						
Onset postexposure	--	10-14 days	1-4 weeks	5-10 days	0-10 days	Almost
Duration	--	4 weeks	1-8 weeks	1-4 weeks	2-10 days	immediately <sup>d</sup>
Symptoms						
Vomiting	None	Infrequent (100 rems); common (200 rems)	100% (300 rems)	100%	100%	100%
Organ most affected	← Hemopoietic system →				Gastroin- testinal tract	Central nervous system
Characteristic effects	None below 50 rems	Moderate leukopenia	Severe leukopenia, purpura, hemorrhage, infection, epilation (>300 rems)		Diarrhea, fever, disturbed electrolyte balance	Convulsions, tremor, ataxia, lethargy
Treatment and Course of Illness						
Critical period (time after exposure)	--	--	1-6 weeks	1-6 weeks	2-14 days	1-48 hr
Therapy	Reassurance	Reassurance hematologic surveillance	Blood trans- fusion, antibiotics	Possible bone marrow transplant	Maintenance of electro- lyte balance	Sedatives
Prognosis	Excellent	Excellent	Guarded	Guarded	Hopeless	Hopeless
Convalescent period	None	Several weeks	1-12 months	Long	--	--
Percentage of vic- tims likely to die	0	0	0-90	90-100	100	100
Time of death after exposure	--	--	2-12 weeks	1-6 weeks	2-14 days	<1-2 days
Cause of death	--	--	Hemorrhage, infection	Hemorrhage, infection	Circulatory collapse	Respiratory failure, brain edema

<sup>a</sup>ORR. Adapted from Glasstone and Dolan [1977], Table 12.105.

<sup>d</sup>Initial phase merges into final phase, death usually occurring in a few hours to about 2 days; this chronology may be interrupted by a very short latent phase.

<sup>b</sup>At the higher doses within this range there may be no latent phase.

begins in week 5 or 6. The course of the illness is a function of the total dose received and individual sensitivity to radiation.

Robert W. Zellmer, "Human Ability to Perform after Acute Sublethal Radiation," *Military Medicine*, Vol. 126, September 1961, pp. 681-687.

Judging from accident, therapy, and Japanese data, the author predicts the performance capability of military personnel after total-body irradiation of  $\leq 600$  rads.

Hour 1. All personnel are 100 percent effective. Vomiting, the only limiting factor, should not interfere with assigned duties.

Day 1. Vomiting subsides. Those who received doses of 500 to 600 rads experience general weakness. Combat efficiency should not be impaired more than 20 percent.

Day 2. Hospitalization is required for all personnel who received doses of 500 to 600 rads, 50 percent of those who received 400 rads, and 25 percent of those who received 300 rads. The efficiency of the unhospitalized 400-rad victims is lowered by 50 percent; of the 300-rad victims, 25 percent.

Day 3. Latent phase begins.

Days 14 to 21. Manifest illness begins. Loss of combat efficiency is total among those who received doses of  $\geq 400$  rads; 75 percent among those who received 300 rads; and 10 percent among those who received 200 rads.

#### Expert Opinion

The studies included in this category contain both factual data and judgments by specialists with considerable firsthand experience in human radiobiology.

George E. Thoma, Jr., and Neil Wald, "The Diagnosis and Management of Accidental Radiation Injury," *Journal of Occupational Medicine*, Vol. 1, August 1959, pp. 421-447.

Drawing on clinical records, the authors set forth the case histories of five hypothetical victims of total-body irradiation. Each history suggests the likely response of a healthy person of the indicated age when exposed to the indicated dose.

1. A 27-year-old male exposed to 53 rads shows no clinical or laboratory symptoms that can be attributed to radiation exposure (representative of group I).
2. A 46-year-old male is exposed to 330 rads. Two hours later he becomes nauseated; the nausea persists and he vomits five times in the next 24 hr. He is weak and fatigued for 4.5 days. Over the next several weeks, he develops infection and manifests reduced platelet and leukocyte counts. Weakness and fatigue gradually diminish, and he returns to light work 5 months after the accident (group II).
3. A 37-year-old male is exposed to 718 rads. Within 45 min he becomes nauseated and retches and vomits violently; those symptoms are accompanied by profuse sweating and extreme weakness. Nausea and vomiting continue for the next 12 hr. From days 4 through 13 he is free of symptoms except for weakness, low-grade fever, and excessive sweating. On day 14 his temperature suddenly rises, indicating infection. By day 23 his general condition has deteriorated badly and he is prostrate and disoriented. Diarrhea accompanied by abdominal cramps begins on day 25 and increases until day 28, when he suffers a massive hemorrhage from the lower gastrointestinal tract. Death follows on day 29 (group III).
4. A 31-year-old male is exposed to 954 rads. Thirty minutes later he becomes nauseated and begins retching and vomiting. In the next 4 hr the nausea and vomiting, accompanied by abdominal cramps, increase in frequency and severity. By 16 hr after exposure, however, the victim is free of symptoms except fatigue and a low-grade fever; he remains in this condition for 5 days. On day 7, his temperature rises and nausea and vomiting recur; platelet and leukocyte counts drop. The symptoms intensify, and the victim dies on day 11 (group IV).
5. Within 8 min after being exposed to 7000 rads, a 37-year-old male begins retching violently and is confused and unable to walk. Vomiting and confusion persist, and prostration is marked after 16 hr. After 21 hr, the victim dies (group V).

Herbert B. Gerstner, "Practical Implications of the Initial Reaction to Penetrating Ionizing Radiation," unpublished manuscript, U.S. Air Force School of Aerospace Medicine, 1970.

Clinical experience with therapy patients receiving doses of up to 300 rems suggests that a sizable population exposed to radiation will cluster in three general groups according to the victims' radiation sensitivity: hypersensitive, normosensitive, and hyposensitive. More will be said about this classification in Sec. 3.

### SECTION 3

#### ANALYSIS OF HUMAN RESPONSE

As we are unable to formulate a direct relationship between performance impairment and level of radiation exposure from the human data available, we examine responses to radiation and derive modeling concepts by analyzing the symptoms and courses of acute radiation sickness.

Using the information described in Sec. 2, we first classify a hypothetical exposed population into response groups, then develop graphs to illustrate individual and population responses. The modeling concepts link radiation dose with (1) the onset and duration of symptoms for individuals, (2) the severity of symptoms experienced by an exposed population, and (3) individual and population responses.

For the sake of consistency, we express all radiation doses as rads absorbed at the internal midpoint of the epigastric region (midline dose). We converted free-in-air exposure levels to absorbed doses by multiplying gamma- and X-ray values by 0.66 [Lushbaugh et al., 1967],<sup>\*</sup> and neutron values by 0.2.<sup>†</sup>

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<sup>\*</sup>This conversion factor is based on a gamma-ray decay of 0.662 MeV Cs-137. Strictly speaking, the conversion factor should vary with photon energy and with the unit of radiation (roentgen or rad). The uncertainties in the data used here, however, make those distinctions insignificant.

<sup>†</sup>This conversion factor accounts for transmission attenuation from the body surface to the interior midline. The 0.2 value is consistent with the theory of fast neutron removal in tissue, where a depth of about 6 in. (15.2 cm) from the body surface to the internal midpoint is assumed. Considering the components of soft tissue, we estimate  $0.1 \text{ cm}^{-1}$  for the macroscopic neutron removal cross section. Use of the 0.2 conversion factor assumes a relative biological effectiveness (RBE) of unity for the acute human response to an absorbed neutron dose. The true RBE value is uncertain, however, and some believe it may be less than unity for considerations of performance impairment [George et al., 1971; Young and Middleton, 1975]. We did not convert estimates of internal doses received by accident victims. We assumed that those estimates took account of gamma-ray doses arising from neutron capture (neutron, gamma) interactions in body tissues.



## RESPONSE GROUPS

The first classification of an affected population into response groups accommodates the well-known variation in sensitivity exhibited by persons exposed to ionizing radiation. As noted in Sec. 2, Gerstner [1970] divided the population into hypersensitives, normosensitives, and hyposensitives. The *hypersensitives* (15 to 25 percent of the population) will show initial symptoms of increasing severity after receiving doses of about 100 rads. The 50 to 70 percent *normosensitives* will show symptoms somewhere in severity between those of the other two groups at about 150 rads. The *hyposensitives*, the remaining 15 to 25 percent, will experience only mild discomfort, if any, at doses beginning around 200 rads.

The second classification, also suggested by Gerstner [1960], groups members of the population by the severity of their symptoms: unaffected, mildly affected, moderately affected, and severely affected.

The *unaffected* group includes exposed persons who show no apparent symptoms of radiation sickness or only signs detectable by clinical tests, such as blood cell counts. When a population is exposed to small doses of radiation, less than 100 rads, the unaffected group would be in the majority. At doses greater than 100 rads, however, the unaffected rapidly would become the minority, and the group might cease to exist at doses of a few hundred rads.

The *mildly affected* are those who become indisposed but not particularly incapacitated, as if experiencing motion sickness. This group may appear at doses under 100 rads but thins out rapidly at doses of 200 to 250 rads. Symptoms begin several hours after exposure, intensify to maximum in several hours, and then ease up over the next 2 days. Seldom do members of this group suffer impairment of physical and mental faculties.

*Moderately affected* persons experience frequent and persistent nausea and vomiting, along with marked weakness, starting 2 to 4 hr after exposure. This group appears at doses of 100 to 150 rads. The nausea and vomiting generally last 5 to 8 hr, during which time the victims' physical and mental capabilities are significantly reduced.

Though less severe, symptoms may linger for several days, having some effect on physical and mental faculties.

Well within 2 hr after exposure, *severely affected* persons will become severely nauseated and begin vomiting. They will be completely incapacitated for 5 to 10 hr or longer depending on the dose. Symptoms may persist for several days, enough to significantly impair physical and mental faculties. This group may appear at doses of 200 rads and will constitute the majority at doses of 800 to 900 rads. At 2000 to 3000 rads, everyone would be in this group.

We use the two classification schemes to link the responses of individuals with the responses of portions of the population.

#### RESPONSE TIMES

For application to combat effectiveness, we are concerned with symptoms of acute radiation sickness from the time of exposure to 6 to 8 weeks afterward, the period during which a victim would either recover or die. Our analysis of the data divides the acute response phase into times and periods, as found in the literature (e.g., Thoma and Wald [1959]; Wald and Thoma [1961]):

- Onset of initial symptoms (time after exposure).
- Initial or prodromal period (duration).
- Latent or asymptomatic period (duration).
- Onset of manifest-illness symptoms (time after exposure).
- Manifest-illness period culminating in recovery or death (duration).

This subsection relates each of those periods or times to absorbed dose for the hyper-, normo-, and hyposensitive response groups. Because the data vary greatly in density and precision, it was inappropriate to apply numerical techniques such as regression analysis to plot the relationships. Instead, we "eyeballed" the data and used reasonable expectations to estimate the extreme-limit values. Where the sources

disagreed, we generally favored accident and therapy data over composite data and expert opinion.

In the graphs that plot each time-dose relationship, precise data points indicate a basis in relatively firm data; ranges (lines connecting data points) indicate some uncertainty; and arrows indicate open-ended values based on quite uncertain data. Symbols represent the four main categories of data and their sources, as follows:

<u>Category</u>	<u>Data Sources</u>
Accident ( $\Delta$ )	Fanger and Lushbaugh, 1967 Hubner and Fry (eds.), 1980 Karas and Stanbury, 1965 International Atomic Energy Agency and World Health Organization, 1961 Lushbaugh, 1969 Thoma and Wald, 1959 Wald and Thoma, 1961 Laumets, 1965
Therapy (+)	Brown, 1953 Miller et al., 1958 Rider and Hasselback, 1968 Saenger et al., 1971 Withers, 1981 (Appendix B of this report)
Composite (o)	Laumets, 1965 Glasstone and Dolan, 1977 <i>NATO Handbook</i> , 1973 Zellmer, 1961 Gerstner, 1958, 1960, 1970
Expert Opinion ( $\times$ )	Fanger and Lushbaugh, 1967 Thoma and Wald, 1959 Wald and Thoma, 1961 Saenger (ed.), 1963 Gerstner, 1958, 1960, 1970

The lack of statistical data on both the distribution of response times for a given radiation dose and the distribution of doses for a given response time makes it impossible to determine precisely what portion of the population the graphed curves represent. A single value from an independent source confirms one of our curves pertaining to the onset time of initial symptoms (described below). Lacking the data to

make similar comparisons for the other time-response curves, we assume that they are reasonable representations.

#### Onset of Initial Symptoms

Figure 3 depicts the relation between the time initial symptoms begin and the absorbed dose. For convenience the data are plotted logarithmically, although the actual dosages, based on accident data, range from 125 to 8800 rads. The dashed line for normosensitives at the lowest doses indicates the conditions under which initial symptoms may never be felt. Otherwise, onset time clearly shortens as the dose increases.

The exact trend at the high end of the dose range is uncertain because of the lack of empirical data. However, Karas and Stanbury's account [1965] of an illness after a dose of 8800 rads is consistent with the high-dose trend in Fig. 3. According to Langham et al. [1965], all persons exposed to several thousand rads can be expected to show the entire range of prodromal symptoms within 5 to 15 min, which is also consistent with the curves in Fig. 3, though actual data at those high ranges are sparse. The curves in the several-hundred-rad range are fairly well supported by the data.

For comparison, Fig. 3 shows the curves obtained by Laumets [1965], who fitted data to a form given by the sum of two exponential terms. Laumets' curve agrees reasonably well with ours at doses of several hundred rads, although we cannot directly compare our three curves with Laumets' single curve, presumably a composite representing the entire population.

To estimate the portion of the population represented by our curves, we can use data on the temporal distribution of the onset of vomiting in 100 male victims [Lushbaugh, 1969]. The mean onset time was  $144 \pm 66$  min after exposure for single doses above 300 rads. We see in Fig. 3 that the normosensitive curve at the 300 rad dose is close to 144 min (2.4 hr), and a standard deviation of  $\pm 66$  min corresponds to values of 1.3 to 3.5 hr, which are well bounded by the hyper- and hyposensitive curves. Assuming an approximately normal distribution,

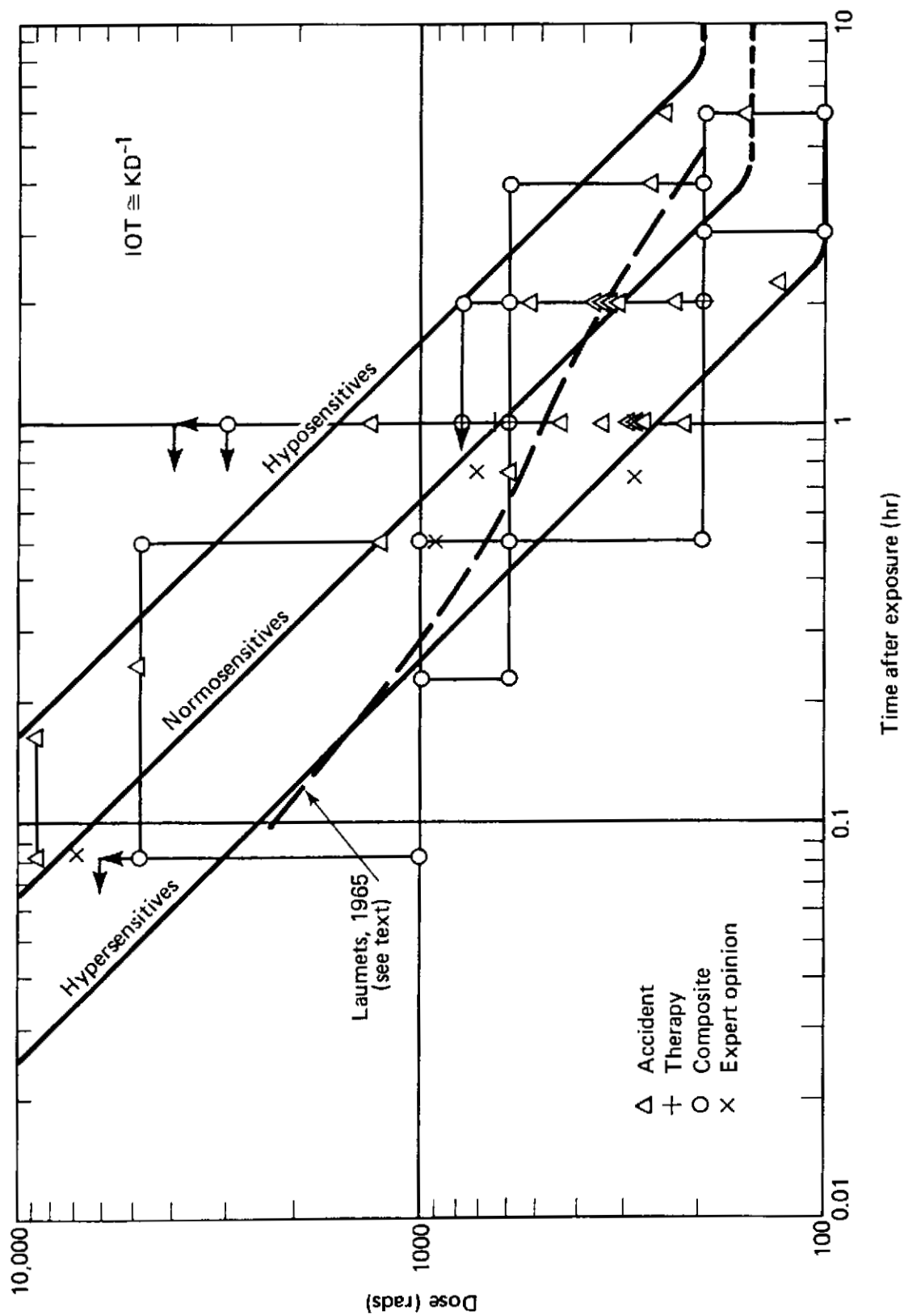


Figure 3. Onset of initial symptoms.

about 92 percent (i.e.,  $1.73 \sigma$ ) of those exposed would fall within the normosensitive range (i.e., between the hyper- and hyposensitive curves).

For each response group, initial onset time IOT (hours) as a function of dose D (rads) can be obtained as follows:

$$\text{IOT}_{\text{hyper}} \approx 250/D \text{ hr}, \quad D \geq 100 \text{ rads}$$

$$\text{IOT}_{\text{normo}} \approx 640/D \text{ hr}, \quad D \geq 150 \text{ rads}$$

$$\text{IOT}_{\text{hypo}} \approx 1600/D \text{ hr}, \quad D \geq 200 \text{ rads}$$

The dosage figures on the right are the threshold dosages at which each group is thought to start showing symptoms [Gerstner, 1970].

#### Initial Period

Figure 4 depicts how the duration of the initial or prodromal period varies with the radiation dose. As suggested by the distribution of data points, it was necessary to make additional assumptions to develop the curves.

We consider anomalous the data indicating initial periods of 4 to 5 hr at doses of 550 and 1200 rads, so we excluded them in plotting the hyposensitive curve. All other accounts of responses to doses of 550 rads and above report the initial period in terms of days, not hours. At those doses, 4 to 5 hr would be more reasonable as the time after onset when initial symptoms peak in severity. Perhaps the data were misinterpreted at some point before the studies were published.

Judging from the curves, the length of the initial period does not vary significantly (more than a decade) with dose. Beyond a few hundred rads, it hardly varies at all, probably because at those lethal doses the initial period is also the final period for many victims. A dose of 325 rads is a reasonable  $\text{LD}_{50/60}$  value for healthy young males who do not receive medical attention [Lushbaugh, 1969].

The dashed curves for hyposensitives and normosensitives suggest that an initial period may be absent for those groups at the lowest doses.

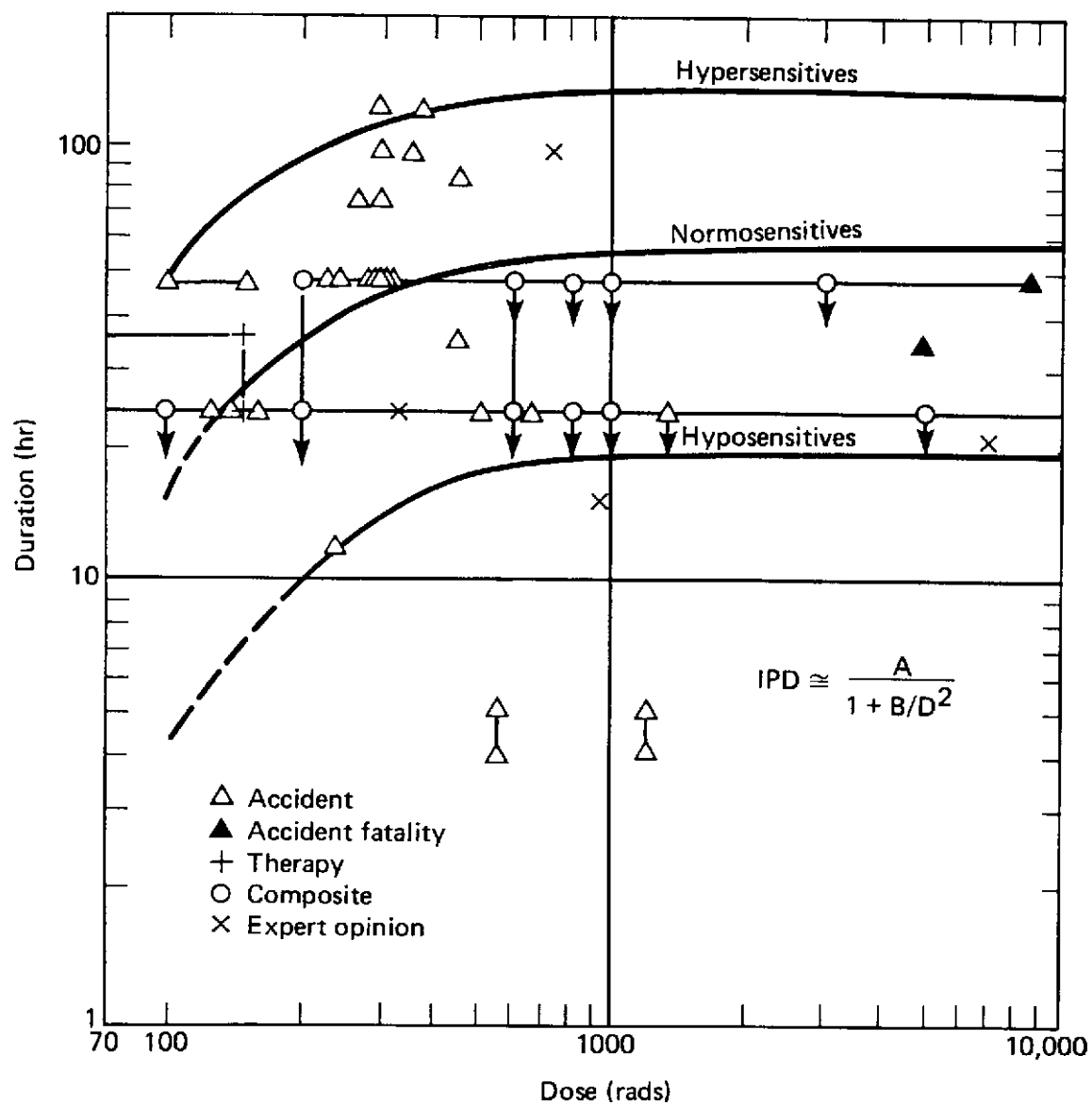


Figure 4. Initial period.

For each response group, the duration of the initial period IPD (hours) as a function of dose D (rads) is obtained as follows:

$$IPD_{\text{hyper}} \approx \frac{130}{1 + \frac{16,400}{D^2}} \text{ hr, } D \geq 100 \text{ rads}$$

$$IPD_{\text{normo}} \approx \frac{58}{1 + \frac{25,800}{D^2}} \text{ hr, } D \geq 150 \text{ rads}$$

$$IPD_{\text{hypo}} \approx \frac{20}{1 + \frac{38,400}{D^2}} \text{ hr, } D \geq 200 \text{ rads}$$

#### Onset of Manifest Illness

Figure 5 depicts the relation between absorbed dose and the number of days after exposure that radiation sickness symptoms recur after a period of apparent remission. Although we did not specifically link the hemopoietic or gastrointestinal syndromes of radiation sickness with the earlier prodromal symptoms, it is clear that they are closely related.

At the lowest doses, hyposensitives and normosensitives may not experience a period of manifest illness, as indicated by the dashed curves. Otherwise, for all groups, onset time decreases as the dose increases. As expected from the rapid deaths and frequent absence of a latent period among victims exposed to large doses, there are fewer data points seen toward the right of the figure. The marked downtrend at the larger doses is mainly supported by the less-firm composite data and expert opinion; we have chosen to express it as a relationship  $\propto D^{-2}$ .

For each response group, the onset time of manifest illness MOT (days) as a function of dose D (rads) can be obtained as follows:

$$MOT_{\text{hyper}} \approx \frac{2.64 \times 10^6}{2 \times 10^5 + D^2} \text{ days, } D \geq 100 \text{ rads}$$



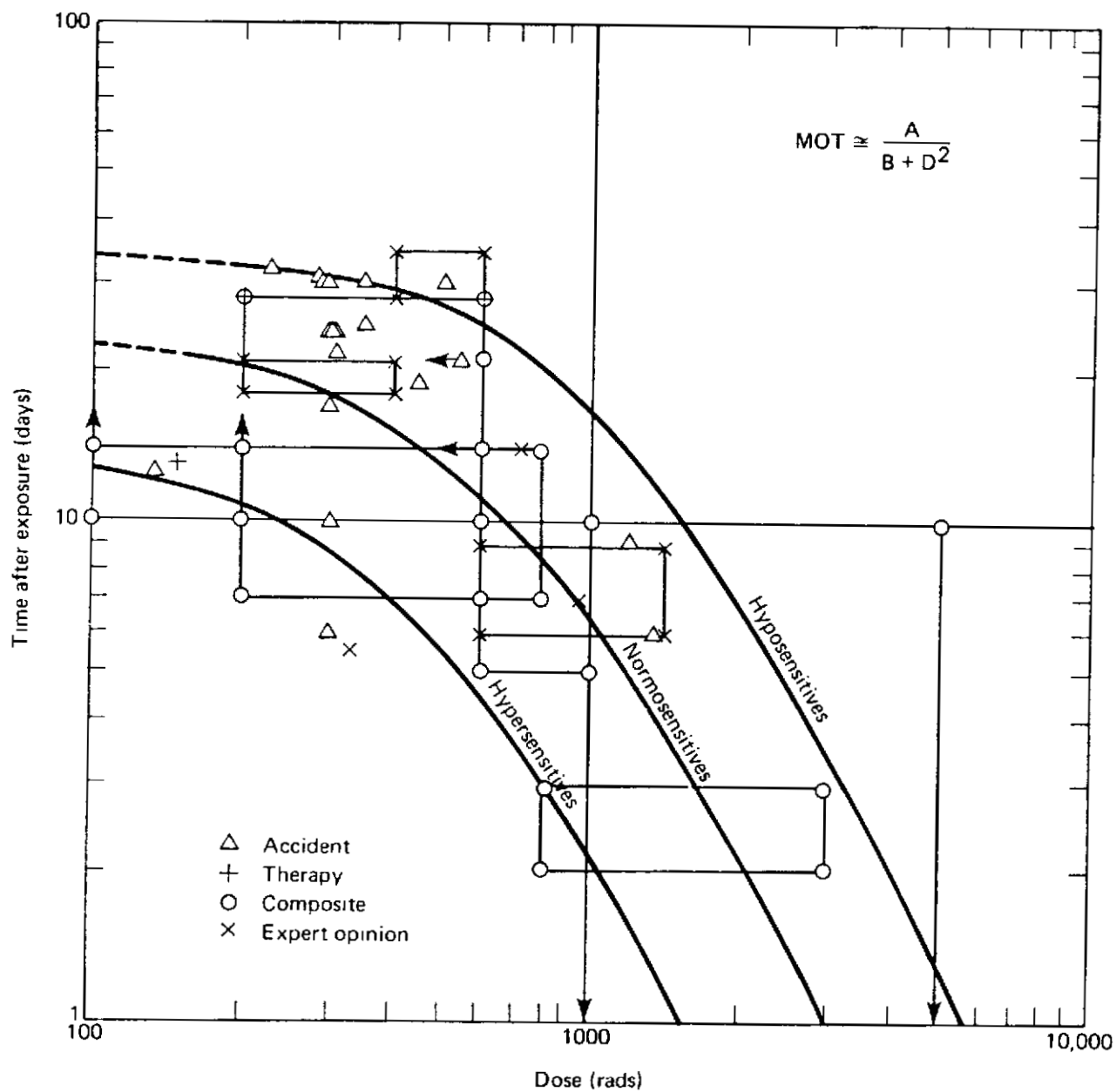


Figure 5. Onset of manifest-illness symptoms.

$$MOT_{\text{normo}} \approx \frac{9 \times 10^6}{4 \times 10^5 + D^2} \text{ days, } D \geq 150 \text{ rads}$$

$$MOT_{\text{hypo}} \approx \frac{34 \times 10^6}{10^6 + D^2} \text{ days, } D \geq 200 \text{ rads}$$

#### Manifest-Illness Period for Victims Who Recover

Figure 6 depicts the relation between absorbed dose and the duration of the manifest-illness period for victims who recover from acute radiation sickness. By "recover" we mean have a clear prognosis of recovery from short-term effects, although some symptoms such as hemopoietic insufficiency or lassitude may persist for weeks or months. Long-term effects of radiation exposure are beyond the scope of this report.

The data of interest are mainly those for sublethal doses of less than a few hundred rads. For those cases, the duration of the manifest-illness period varies no more than a decade. The straight lines indicating the period's increase with dose for each response group are based on the trend of the data points and the requirement that the period vanish at 0 rads. However, the lines are truncated to begin at the threshold dose assumed for each response group.

Using the data points representing fatalities at the high doses, we constructed a dashed curve to suggest a rough boundary between recovery and death (the  $LD_{50/60}$  line).

For each response group, the duration of the manifest-illness period ending in recovery MDR (days) as a function of dose  $D$  (rads) can be obtained as follows:

$$MDR_{\text{hyper}} \approx 0.14D \text{ days, } D \geq 100 \text{ rads}$$

$$MDR_{\text{normo}} \approx 0.067D \text{ days, } D \geq 150 \text{ rads}$$

$$MDR_{\text{hypo}} \approx 0.02D \text{ days, } D \geq 200 \text{ rads}$$

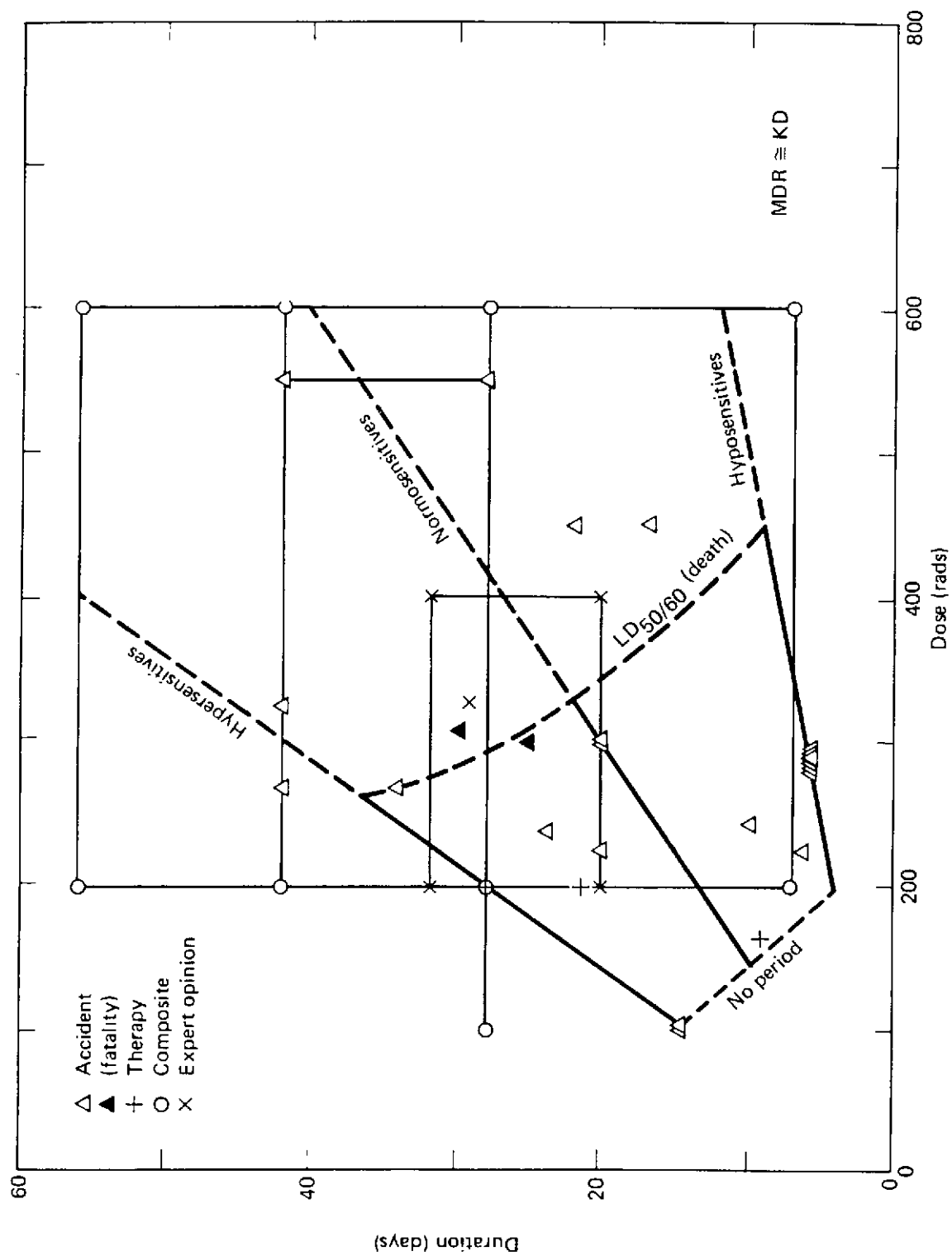


Figure 6. Manifest-illness period for victims who recover.

#### Manifest-Illness Period for All Victims

Figure 7 depicts the relation between absorbed dose and the duration of the manifest-illness period. The curves for victims who recover reproduce the dashed portions of Fig. 6 extending beyond the LD<sub>50/60</sub> line. At doses above a few hundred rads, the manifest-illness period clearly decreases with dose. The straight 45 deg lines through the logarithmic plots indicate that trend. Those lines fit the data fairly well; further precision is impossible.

We assume that a hyposensitive victim would, if subjected to a lethal dose, experience a manifest-illness period longer than the median before death. Similarly, a hypersensitive person would die sooner than the median time after receiving a lethal dose. The normosensitive curve corresponds to the median.

The substantial overlap in the two sets of curves reflects the uncertainty of the data regarding the boundary between recovery and death as related to dose.

For each response group, the duration of the manifest-illness period ending in death MDD (days) as a function of dose D (rads) can be obtained as follows:

$$MDD_{\text{hyper}} \approx 6,650/D \text{ days, } D \geq 100 \text{ rads}$$

$$MDD_{\text{normo}} \approx 12,000/D \text{ days, } D \geq 150 \text{ rads}$$

$$MDD_{\text{hypo}} \approx 20,000/D \text{ days, } D \geq 200 \text{ rads}$$

#### Entire Response

Using the information in Figs. 3 through 7, we plotted the relationship of all temporal aspects of the acute radiation response to absorbed dose. Figure 8 shows the normosensitive curve and identifies each time or period depicted along its length, as follows:

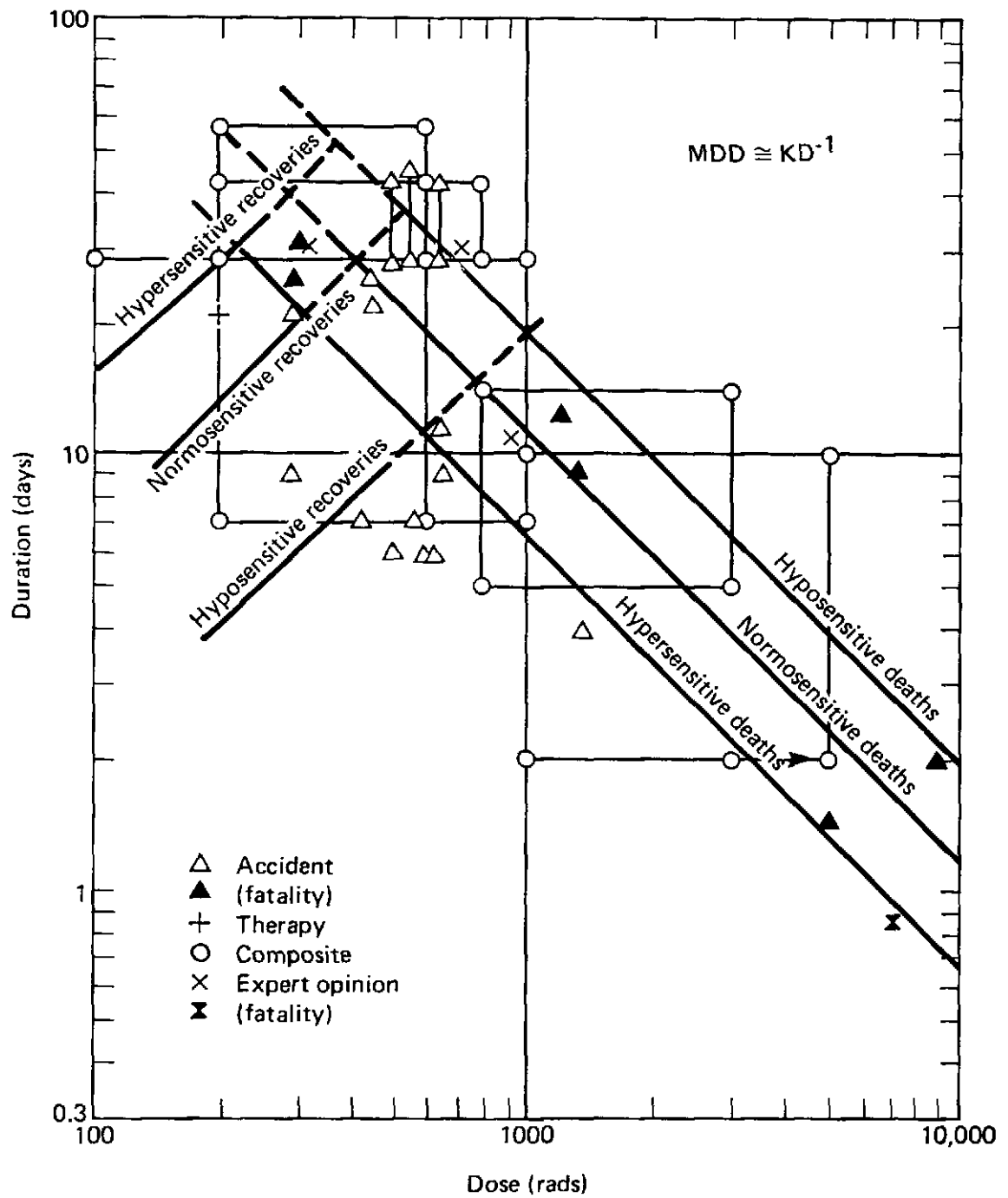


Figure 7. Manifest-illness period for all victims.

- $t_1$  = onset time of initial symptoms (IOT)  
 $T_1$  = initial period (IPD)  
 $T_R$  = latent period (MOT - IOT)  
 $t_2$  = onset time of manifest illness (MOT)  
 $T_{2,r}$  = manifest-illness period ending in recovery (MDR)  
 $T_{2,d}$  = manifest-illness period ending in death (MDD)

As Fig. 8 shows, the initial period lasting 3 to 48 hr after exposure is followed by a period of remission ( $T_R$ ) that increases as the

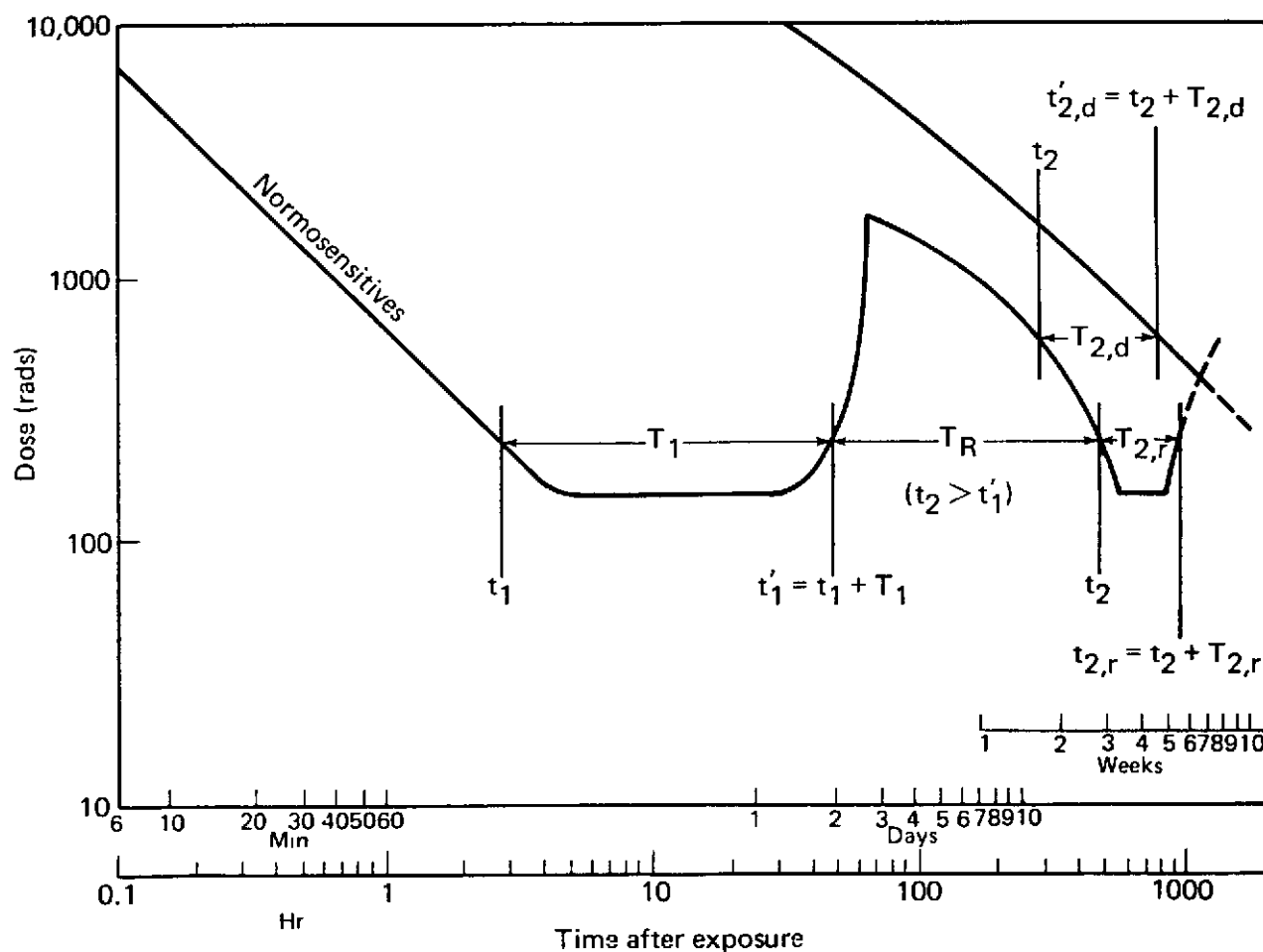


Figure 8. Entire acute radiation response: relation of time and dose for normosensitives.

dose becomes smaller, for doses under 1700 rads. The remission period is formed by the boundaries and intersection of the  $t_1'$  and  $t_2$  curves for  $t_2 > t_1'$ , so its duration is determined indirectly rather than directly from data. The sharp corners in the plot are simply a consequence of combining the individual time relationships; such abrupt discontinuities would not be expected in a thorough statistical analysis.

Figure 9 shows the curves for all three response groups for comparison. There are substantial differences in all times and periods, although the log-log plot somewhat obscures the differences in the times of death and recovery.

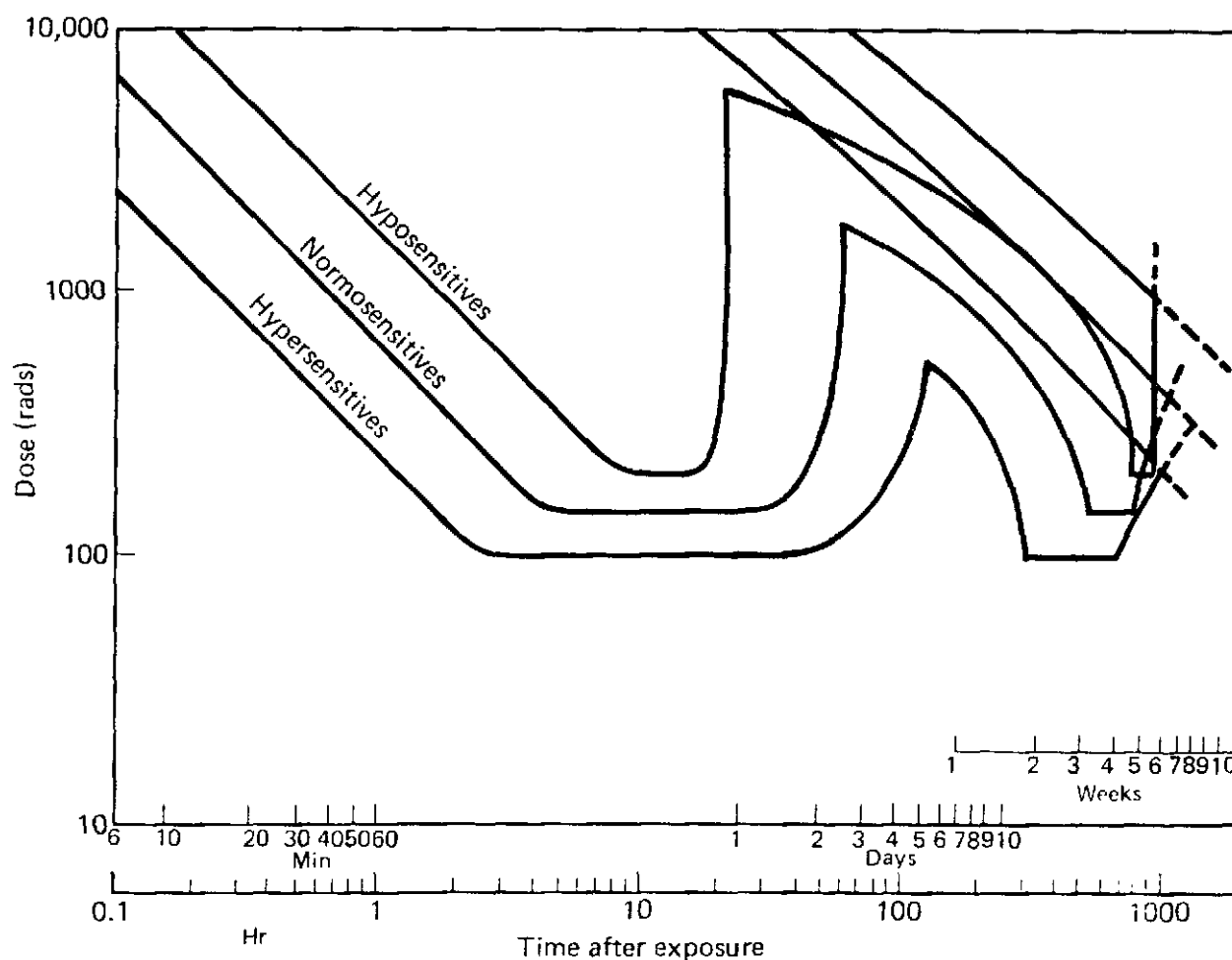


Figure 9. Entire acute radiation response: relation of time and dose for all response groups.

## RESPONSE SEVERITY VERSUS TIME

For tactical planning, we need to estimate *how long* after a nuclear attack *how many* military personnel will be able to perform *which* battle-field tasks. It is thus important to link the information presented above on the temporal occurrence of radiation sickness symptoms with the distribution of their severity. The literature provides no specific evidence for a time-severity response profile. It does, however, offer general guidance for developing such a profile for the "typical person" [Gerstner, 1958, 1960], which is depicted in Fig. 10.

The existence of separate prodromal and manifest-illness periods is well supported for doses of more than 100 to several thousand rads [Brown, 1953; Miller et al., 1958; Thoma and Wald, 1959; Wald and Thoma,

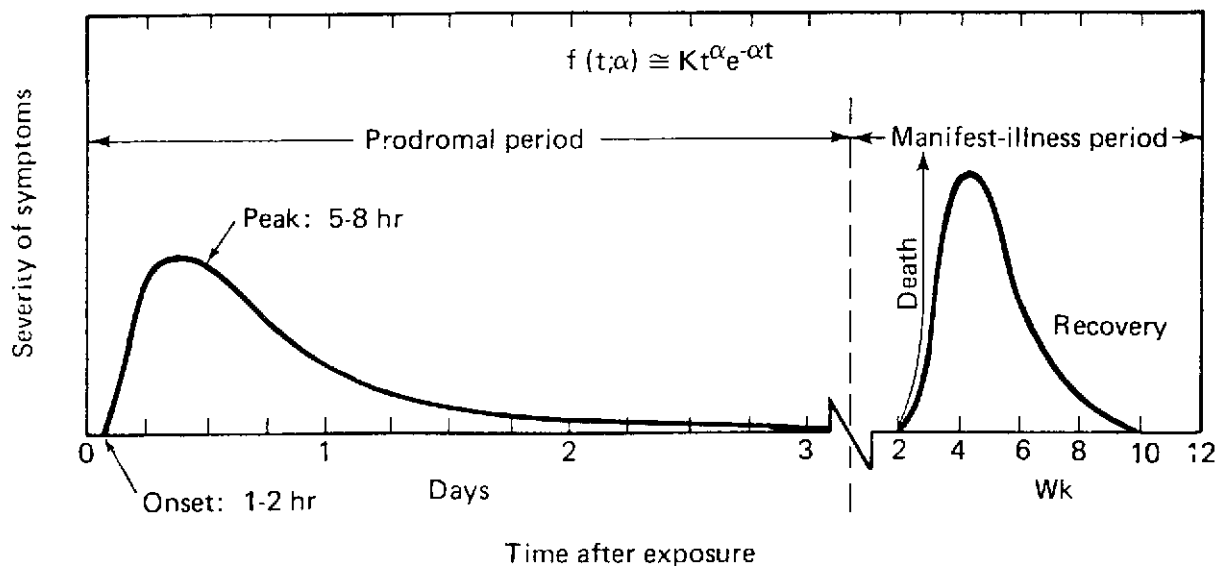


Figure 10. "Typical" (normosensitive) time-severity response profile (dose, ~100 to 400 rads).



1961; and Lushbaugh, 1967, 1969].\* At lower doses of ~100 to 400 rads, represented in Fig. 10, prodromal symptoms begin ~1 to 2 hr after exposure, peak 5 to 8 hr postexposure, and subside about 2 to 3 days postexposure.

For low doses (~100 to 135 rads), Miller et al. [1958] place the manifest-illness period at 3 to 4 weeks postexposure, when hemopoietic depression characterized by bleeding, infection, and pancytopenia becomes clinically significant. Based on reactions to therapeutic doses of 300 rads after about 15 min, Rider and Hasselback [1968] estimate the time of maximum hemopoietic depression at 25 to 30 days postexposure. Gerstner's time-severity profiles [1958] resemble those in Fig. 10 in suggesting that symptoms are more severe in the manifest-illness period than in the prodromal period. It is not clear, however, whether Gerstner is comparing a single symptom or the overall illness reflected by a number of symptoms in the two periods.

The profile in Fig. 10 can be conveniently expressed by the relationship

$$f(t; \alpha) \cong Kt^{\alpha} e^{-\alpha t},$$

where  $K$  is a peak normalizing constant and  $\alpha$  is the shape parameter.  $K$  adjusts the response amplitude, i.e., percentage of exposed population, and  $\alpha$  determines the peak position. Insofar as the peak can shift with dose,  $\alpha$  can be shown as a function of dose. Figure 11 illustrates the peak shift. Assuming that initial symptoms subside to 1/10 of their peak value (by an assumed measure) 48 hr after exposure, we estimate a time  $t_{1/10}$  of 48 hr for the abatement of symptoms. Figure 11 determines  $\alpha$  for the prodromal period depicted in Fig. 10 by selecting the appropriate ratio of  $t_{1/10}$  to  $t_{\max}$ , the time initial symptoms

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\* However, as noted earlier, the prodromal period may blend into the manifest-illness period for victims exposed to doses greater than 1000 rads. Prodromal symptoms may begin as early as 5 to 15 min post-exposure [Lushbaugh, 1969; Langham (ed.), 1967], peak in intensity after about 30 min, and persist for several days, gradually merging with a fatal vascular or gastrointestinal syndrome.

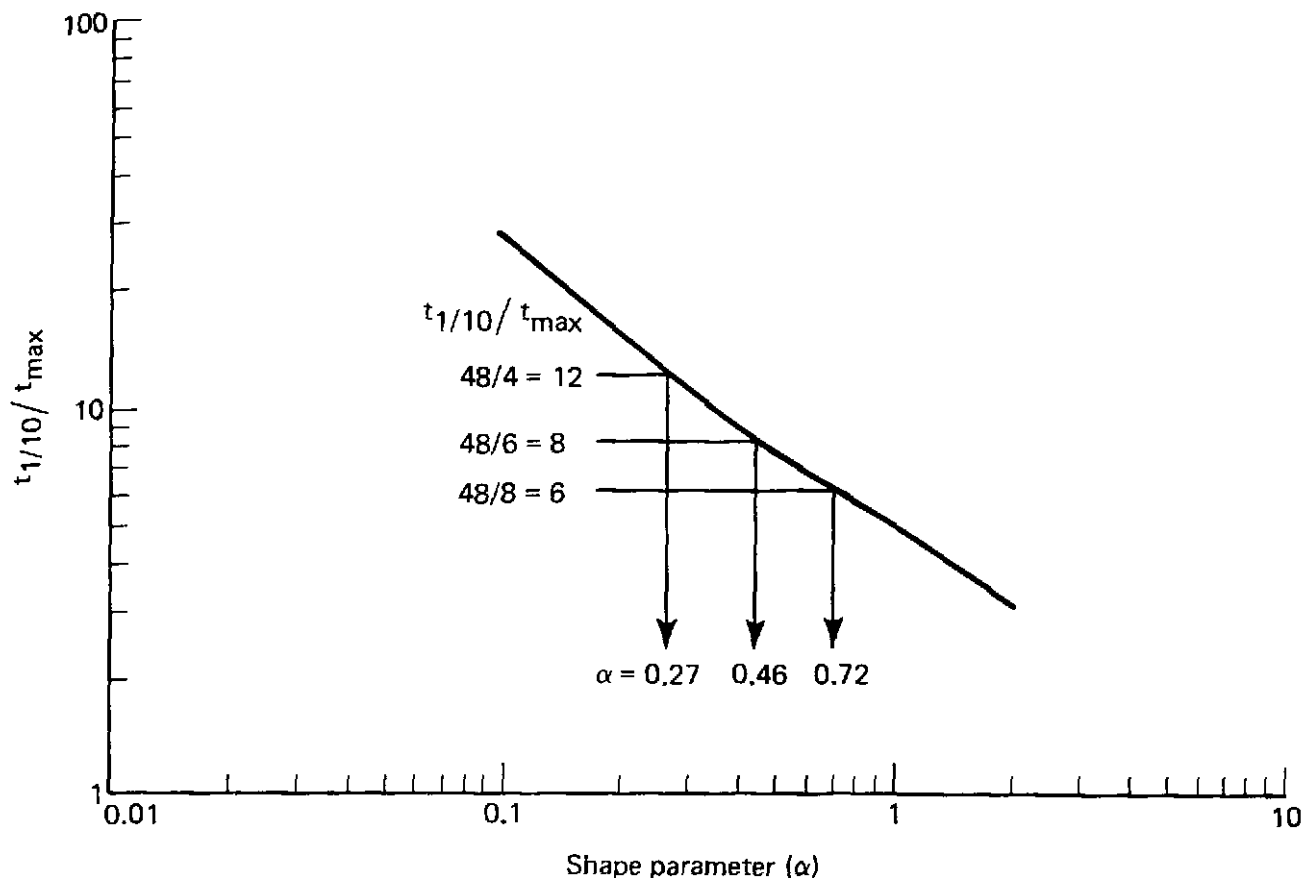


Figure 11. Shape parameter for peaking and abatement of symptoms.

peak. For illustration, three different  $t_{\max}$  values are assumed (reflecting three doses): 4, 6, and 8 hr. A time-intensity response profile can be similarly developed for the manifest-illness period.

Figure 12 adds the dimension of symptom severity to the dose and time relationships plotted earlier. The shaded areas indicate the onset, peak, and abatement of symptoms in the prodromal and manifest-illness periods. The wide shaded area at the highest doses depicts the profile for victims whose prodromal period merges into a fatal manifest-illness period.

To summarize the results of this section so far, Fig. 13 shows a contour plot of the normosensitive response to radiation relating dose, time, and symptom severity. Here symptom severity refers to the

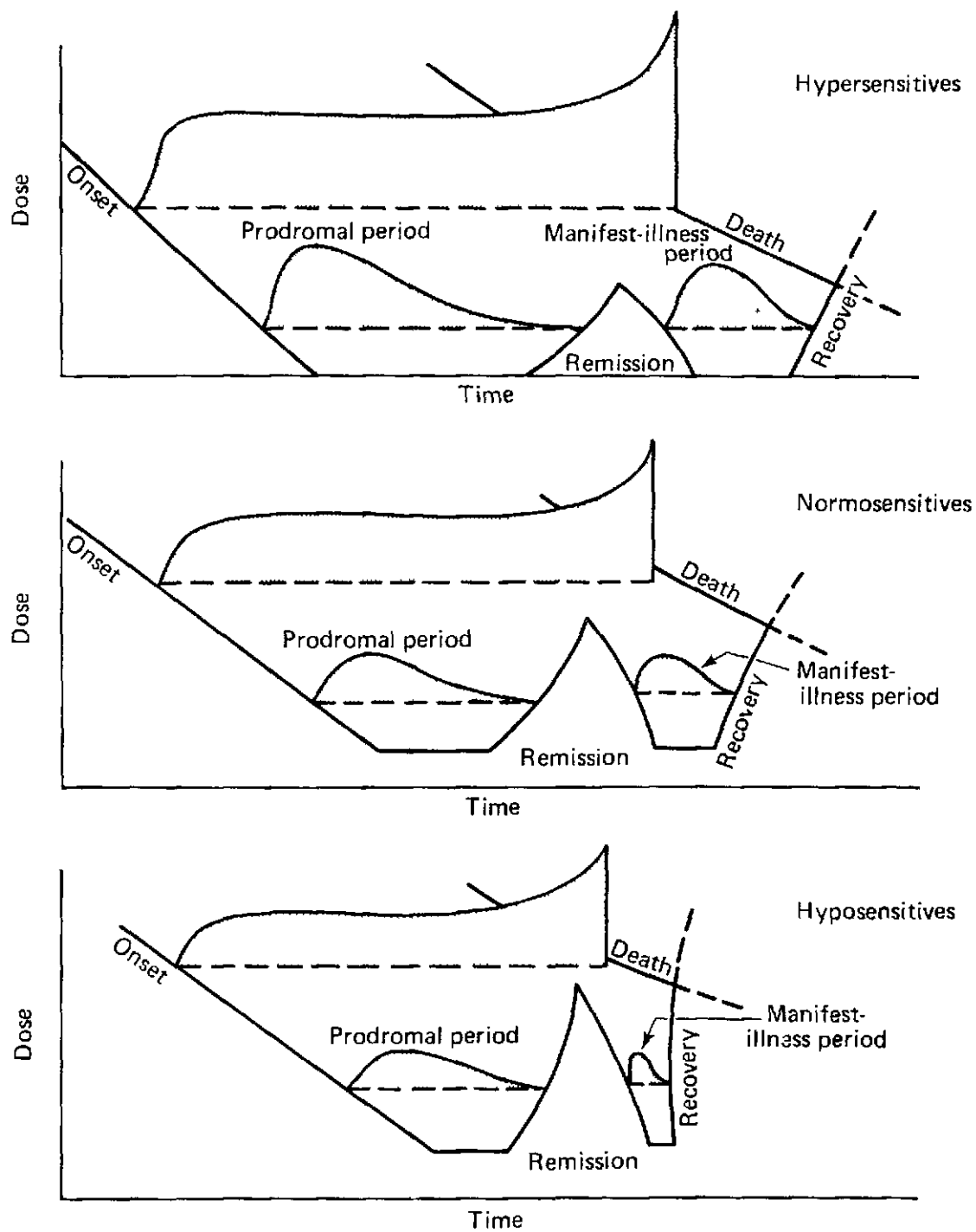


Figure 12. Acute radiation response for all groups: dose-time-severity profile.

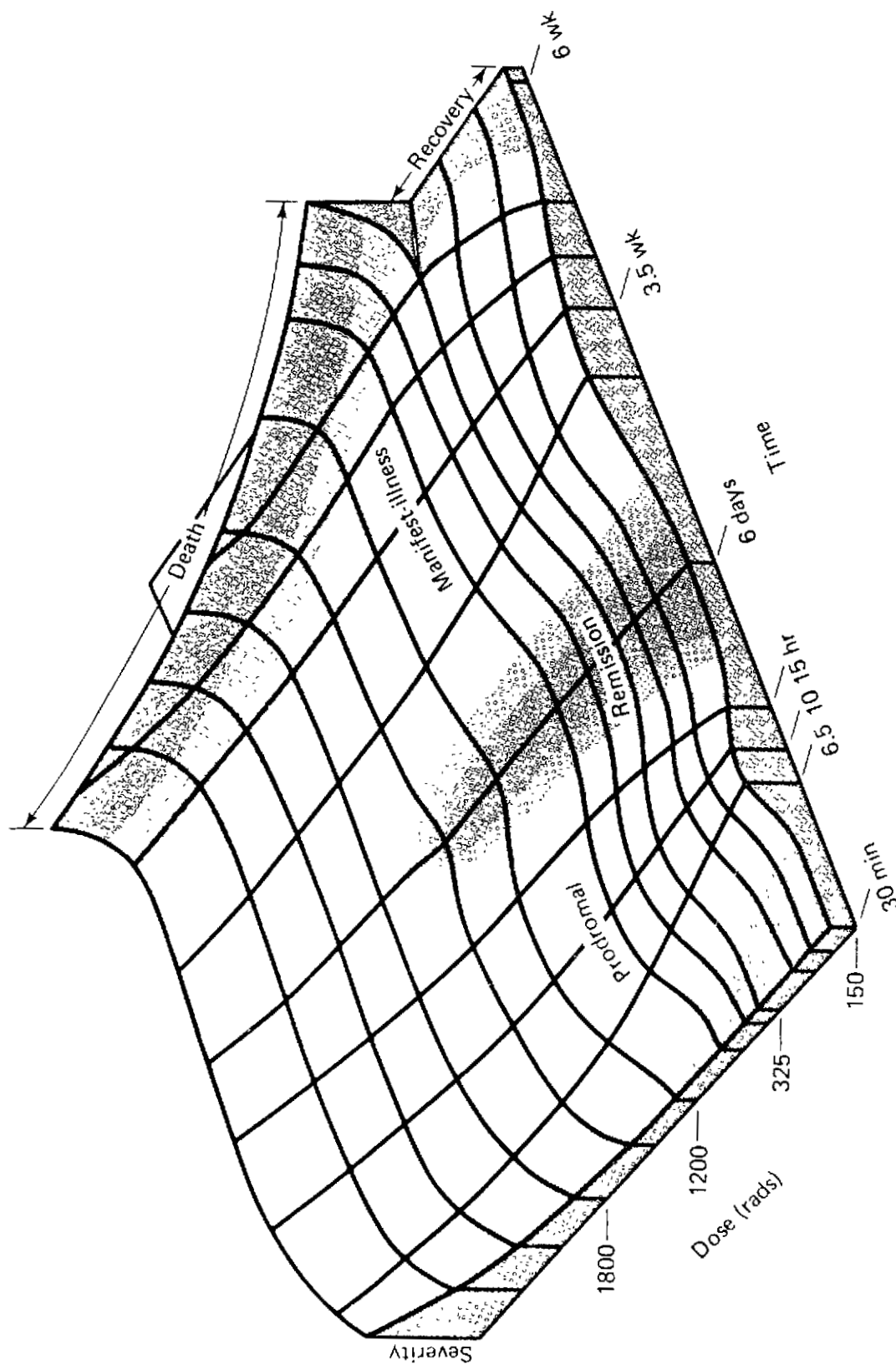


Figure 13. Acute radiation response for normosensitives: contour plot of dose, time, and symptom severity.

combination of symptoms reflecting radiation sickness, not a single symptom. Analogous contours could be developed for particular symptoms or syndromes such as nausea, vomiting, fatigue, diarrhea, and hemopoietic depression, as described by Brucer (comp.) [1959]. The ultimate goal, of course, is to develop a set of contours to project performance impairment for a given radiation dose.

#### POPULATION RESPONSE

We now consider the prodromal response in a large population exposed to varying doses of ionizing radiation. Figure 14 plots, by dose, rough percentages of the population who might (1) experience nausea and vomiting and (2) fall in each response group classified by severity of symptoms. For a given dose, the component response groups add up to the total population (100 percent). The curves are only suggestive; the lack of data, especially for doses above a few hundred rads, makes anything approaching statistical significance impossible.\*

Based on a study of 100 cases (93 therapy patients and 7 accident victims), Lushbaugh et al. [1967] relate clinical responses to TBI doses in a probit analysis of effective doses needed to produce gastrointestinal and other systemic responses. They develop probit relationships for anorexia, nausea, vomiting, fatigue, diarrhea, and death--two sets each, assuming normal and log-normal distributions of the data. We used the relationships for nausea and vomiting assuming a normal distribution:

$$\text{Nausea: } p(D) = 0.008D + 3.837 ,$$

$$\text{Vomiting: } p(D) = 0.008D + 3.588 ,$$

where D is the dose in rads and the numbers represent probit units. Obtaining cumulative distributions with the logistic formula

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\*The contents of Fig. 14 and our discussion rely heavily on Gerstner [1958, 1960, 1970], Lushbaugh et al. [1967], Lushbaugh [1969], Langham et al. [1965], and Langham (ed.) [1967].

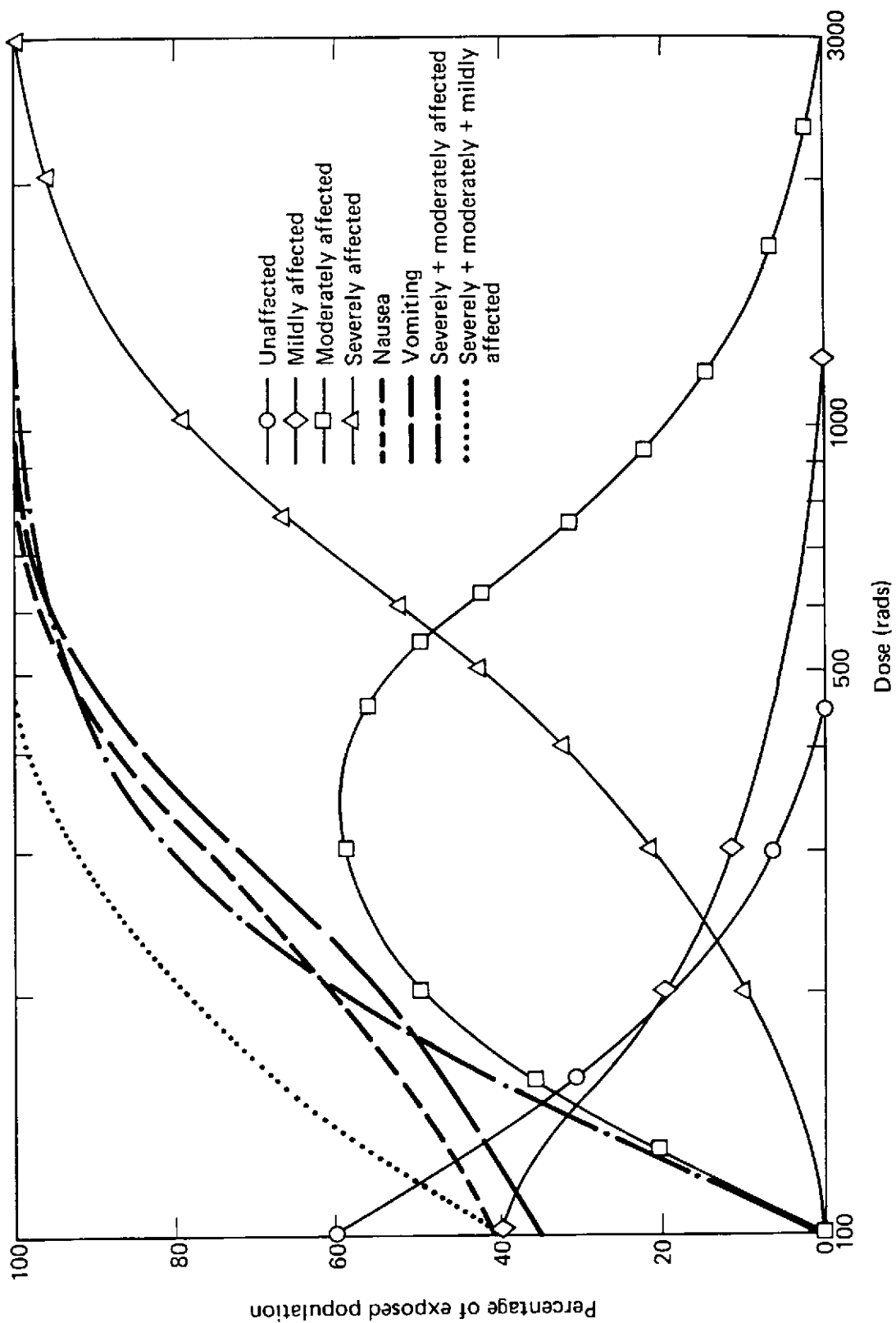


Figure 14. Distribution of radiation response in an exposed population.

$$p(D) = \frac{1}{1 + \exp \{- [p(D) - 5]\}} ,$$

we plotted the curves for nausea and vomiting in Fig. 14. The  $p(D)$  function is of a sigmoid form and nearly indistinguishable from a cumulative normal distribution [Kruskal and Tanure (eds.), 1978]. For a dose of 100 rads, the cumulative values for nausea and vomiting are 41 and 35 percent, respectively; the corresponding values assuming a log-normal distribution--49 and 42 percent for nausea and vomiting, respectively--do not differ greatly, considering the imprecision of the data.

Gerstner [1960] estimates that about 50 percent of the exposed population would be affected by a midline absorbed dose of ~100 rads. Since he is judging from the experience of therapy patients, who were already ill, we think that estimate is slightly high for the general population. We estimate that 40 percent of the population would be affected at 100 rads. At that dose Fig. 14 classifies all responses as mild, so the remaining 60 percent of the population would be unaffected. The peaking of the mild response curve at about 100 rads cannot be specifically verified. However, Gerstner asserts that close to the threshold dose of 70 rads\* the initial reaction, if any, takes the mild form of brief spells of fatigue, anorexia, and nausea. Glasstone and Dolan [1977] also doubt that clear-cut prodromal reactions would show up in a population exposed to less than around 70 rads.

In the dose rate of 130 to 200 rads, Gerstner [1960] uses therapy data to estimate the following response pattern: unaffected, 20 percent; mildly affected, 20 percent; moderately affected, 50 percent; and severely affected, 10 percent. Miller et al., [1958; Levin et al., 1959]. Figure 14 reflects that distribution pattern at a dose of 200 rads. Gerstner further asserts, drawing on Brucer (comp.) [1958] and Miller et al. [1959], that the response pattern persists at higher doses.

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\* This and similar dose figures are not precise but are the nearest dose equivalents of round-number free-in-air doses.

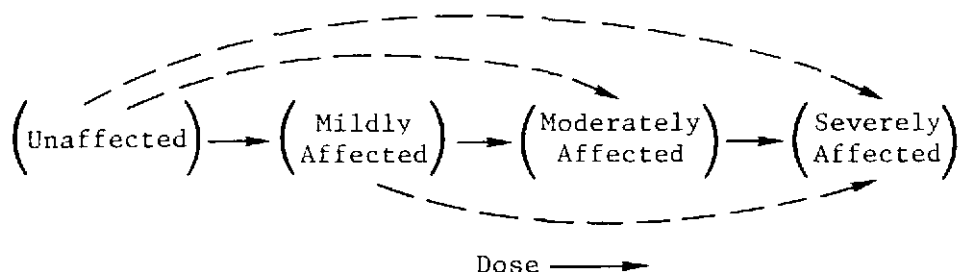
perhaps up to 540 rads: each person displays the severity of reaction peculiar to his response group.

Later, however, Gerstner [1970] proposes a different response pattern in which hyposensitives (~20 percent of the exposed population) experience the severest symptoms after doses of about 350 rads; normosensitives (60 percent of the population) experience the severest symptoms after about 340 rads; and hypersensitives (20 percent) experience full severity after about 300 rads. Gerstner's suggestion of an apparent plateau in response severity above doses of 300 to 350 rads is not specifically supported by the rest of the literature we examined. On the contrary, the popular view is that severity increases with dose until a point of total incapacitation at doses of several hundred to a few thousand rads [Shelberg and Ulberg, 1967; Glasstone and Dolan, 1977; NCRP, 1974]. In the dose range of 1000 to 10,000 rads, it is difficult to infer any precise trend regarding symptom severity from the data, primarily accident data [Hemplemann et al., 1952; Thoma and Wald, 1959; Karas and Stanbury, 1965; Fanger and Lushbaugh, 1967; Lushbaugh, 1969; Hubner and Fry (eds.), 1980]. The recent study by Cairnie and Robitaille [1980] points out the same difficulty.

Although Gerstner himself did not make the connection [1970], the response pattern in Fig. 14 is consistent with Gerstner's percentages for hypo-, hyper-, and normosensitives above if we assume that at doses of 300 to 350 rads, hyposensitives include both the unaffected and mildly affected, the normosensitives include the moderately affected, and the hypersensitives include the severely affected.

Figure 14 shows that the percentages of unaffected, mildly affected, and moderately affected drop above a certain dose, while the percentage of severely affected rises correspondingly. Over the 100 to 350 rad range, the percentage of the moderately affected rises. The pattern thus presumes that individuals in an exposed population shift to increasingly severe response categories with dose, as illustrated below:





Again, no precise empirical evidence exists to verify the sequence above, let alone the sequence related to dose. However, it seems reasonable that above a certain dose (here assumed to be 3000 rads) essentially all persons in an exposed population will be severely affected by radiation, regardless of their sensitivity classification (hypo-, hyper-, normosensitive).

The response distribution at the highest doses in Fig. 14 seems to be borne out by specific accident accounts. A victim exposed to 1200 rads [Hubner and Fry, 1980: 91-104] showed more than a mild response [Hemplemann et al., 1952], as did two others who received doses of 4500 rads [Fanger and Lushbaugh, 1967] and 8800 rads [Karas and Stanbury, 1965]. Assigning a specific sensitivity classification to any of those victims is of course impossible.

The combined plot for severely and moderately affected in Fig. 14 resembles plots for nausea and vomiting in Lushbaugh et al. [1967]. Thus we surmise that the mildly affected would probably experience nausea but not severe vomiting.

#### INDIVIDUAL-POPULATION RESPONSE MODEL

Here we attempt to link the individual responses described above for hyper-, normo-, and hyposensitives with the population responses described for the unaffected through severely affected groups. A heuristic approach is necessary to compensate for deficiencies in the empirical data. The dimensions of dose and symptom severity are related only for the initial period as a whole; the variable time dimension is omitted because of insufficient data.

Earlier in this section we postulated the dosages at which each sensitivity group begins to respond to radiation: hypersensitives, 100 rads (dose  $D_1$ ); normosensitives, 150 rads ( $D_2$ ); and hyposensitives, 200 rads ( $D_3$ ). Figure 15 extends the responses presented earlier for individuals in those groups, expressing each group's response in terms of the percentage of incapacitation as a function of dose above the threshold. Each curve depicts a cumulative increase; reaching total incapacitation at doses  $D'_1$ ,  $D'_2$ , and  $D'_3$  for hyper-, normo-, and hypo-sensitives, respectively. The exact form of the cumulative function is unknown; variations in response for each sensitivity group might be normally or log-normally distributed with respect to dose. Moreover,

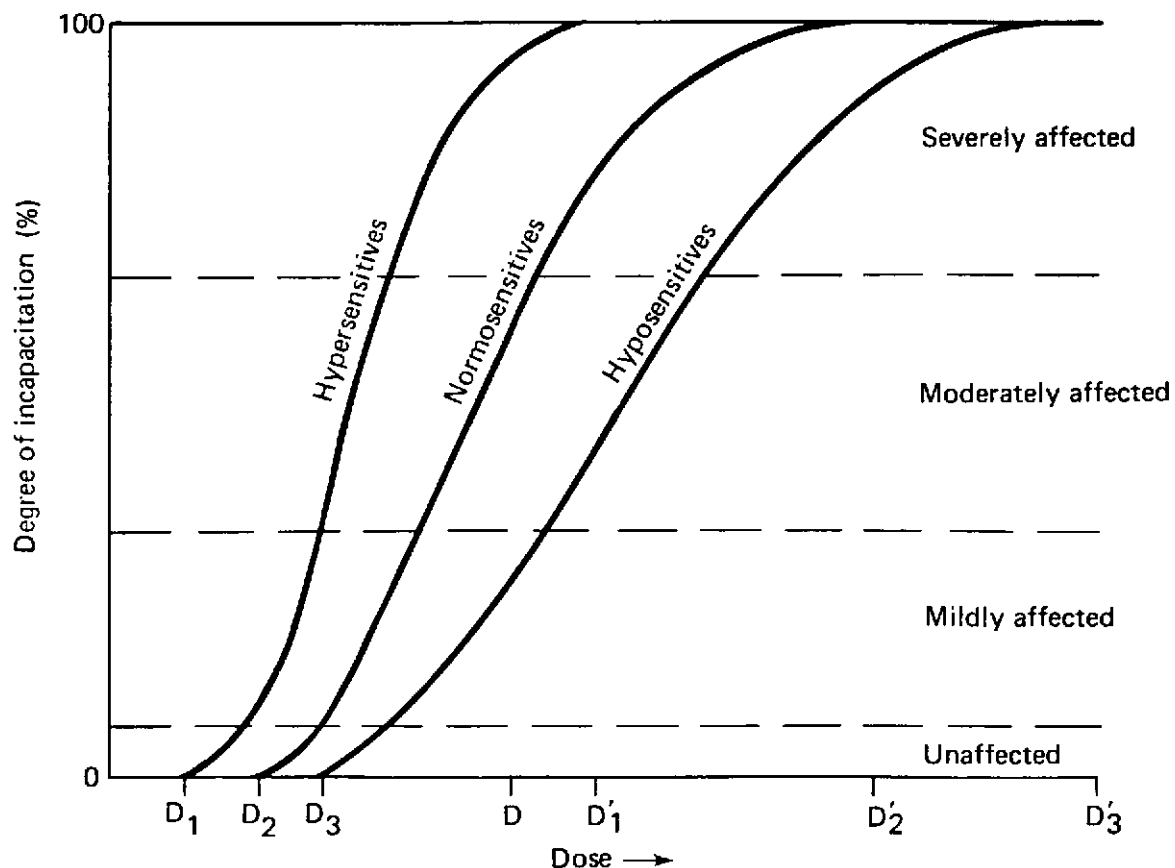


Figure 15. Individual response in initial period.

individuals in any group might well respond differently from the group norm. The curves slope more gently as sensitivity decreases, suggesting greater response variance with dose. That pattern is consistent with nonradiation types of insults [Lushbaugh, 1981].

We have divided the vertical scale representing degree of incapacitation into four regions corresponding to the population response groups: unaffected, and mildly, moderately, and severely affected. The somewhat arbitrary regional division is based on the following assumptions:

<u>Population Response Group</u>	<u>Degree of Incapacitation (%)</u>
Unaffected	0-10
Mildly affected	10-30
Moderately affected	30-60
Severely affected	60-100

Further investigation of incapacitation--perhaps applying a modified version of the Karnofsky scale<sup>\*</sup>--should enable better estimates of physical and mental impairment.

Figure 16 uses the assumptions in Fig. 15 to relate individual sensitivity with population group response as a function of dose. The plots illustrate our basic presumptions: that the dose required to produce the severest symptoms and maximum incapacitation increases with decreasing individual sensitivity, and that an exposed population becomes increasingly incapacitated the higher the dose. The curves are not intended to express a quantitative assessment but to depict our modeling concept linking individual and population responses.<sup>†</sup>

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<sup>\*</sup>A scale in increments of 10 percentage points for gauging the "performance status" of persons with illnesses such as cancer.

<sup>†</sup>Appendix C presents basic algebraic relationships underlying Figs. 15 and 16 that need to be established in order to develop the model in greater detail.

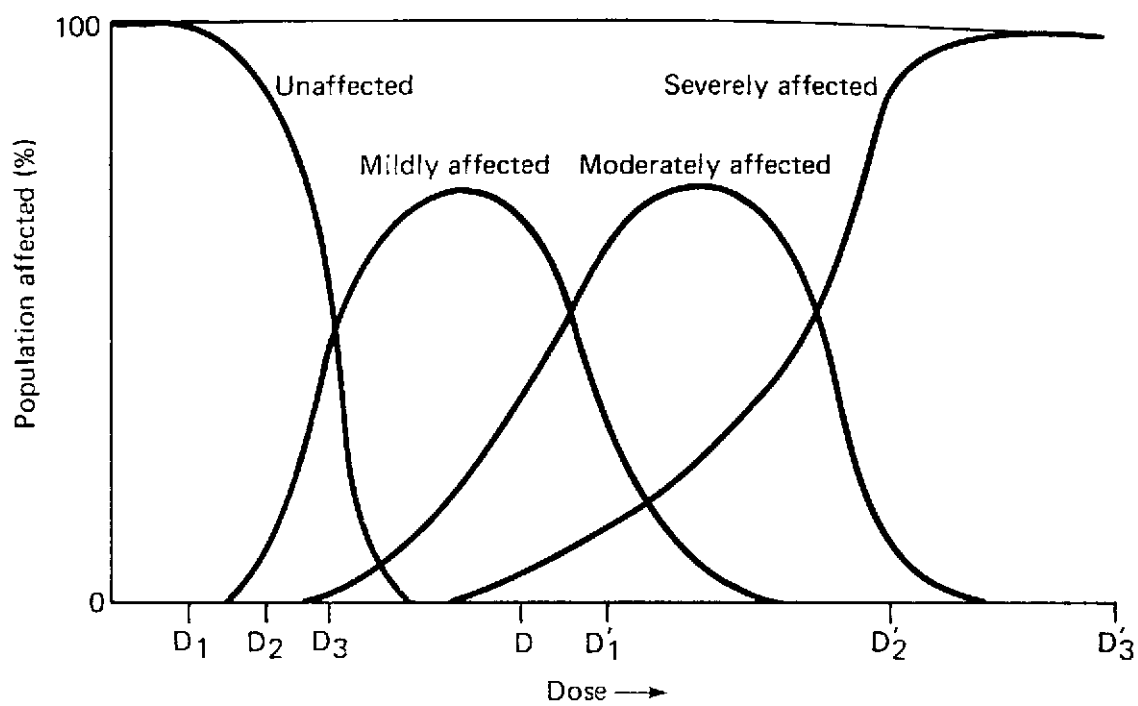


Figure 1b. Population response in initial period.

## SECTION 4

### CONCLUSIONS AND RECOMMENDATIONS

The limited data permit the following general conclusions:

1. Fairly specific radiation sickness symptoms can be related to absorbed dose and time after exposure for healthy adults.
2. It is reasonable to divide an exposed population into the following response groups, based on their sensitivity to radiation: hyposensitives, normosensitives, and hypersensitives.
3. It is reasonable to divide an exposed population into the following groups, based on the severity of their symptoms: unaffected, mildly affected, moderately affected, and severely affected.

We derive a hypothetical model that portrays radiation response along the dimensions of dose, time, and severity of symptoms. The model takes account of individual sensitivity to radiation and illustrates the onset and duration of both initial (prodromal) and manifest-illness periods for any given dose. We also suggest a model that links individual and population responses in the initial period as a function of dose.

To develop the models further, we need a much better understanding of the relation between radiation exposure and subsequent illness as a function of time. We need more data from noninvasive clinical studies on how therapeutic radiation affects patients' minds and bodies. Any new accident data should be carefully studied. It may be possible to make better use of data on irradiated animals, and to clarify the relation of animal behavior after irradiation to human behavior under similar conditions. It has been suggested that other animals respond more like humans in the initial postexposure period than the Rhesus

monkeys frequently used in experiments. Reexamination of the Japanese data on atomic bomb survivors may be worthwhile; the questionnaires they completed contain much detail.

Once the connection between radiation exposure and sickness is sufficiently well understood, it should be possible to make more definitive statements about how human performance will be affected by radiation. The role of such factors as psychological state, age, and training should also be considered. A study of specific military tasks and analysis of the human effort required would help correlate radiation sickness with combat performance.

Even when performance impairment is correlated with radiation exposure for *individuals*, however, questions will remain about the effectiveness of *units* in accomplishing their combat missions. For investigating how individual performance impairment influences unit effectiveness, several computerized models of military unit performance could be adapted to simulate the incapacitation effects of nuclear radiation. We recommend that such parametric studies be done, with the object of assessing the combat effectiveness of military units that have been at least partially exposed to doses greater than 100 rads. Models of small units (tank crews, artillery batteries, and the like) are needed for evaluating the speed, accuracy, and endurance with which crew members perform their assigned tasks. Then, links can be made to the activities of larger units such as battalions, divisions, and regiments.

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## Appendix A

### REVIEW OF JAPANESE ATOM BOMB DATA

The experience of the atom bomb survivors in Hiroshima and Nagasaki cannot be directly related to battlefield performance impairment. Nevertheless, data on exposure levels and symptoms constitute a potentially valuable source to be tapped in developing our response model.

We are primarily interested in correlating the doses that victims received with the nature and temporal occurrence of their prodromal symptoms. On the face of it, the Japanese data appear of little use to that purpose. In both Japanese cities, radiation levels attenuated greatly with distance. In each annulus of area from the blast center, symptomatic responses were not differentiated but doses differed markedly. Thus the data would not permit correlations of symptoms with dose as precise as those permitted by the therapy and accident data.

The temporal correlations possible are similarly imprecise. Data were collected from victims no sooner than 20 days after the bombings. By that time, survivors recollected the occurrence of their symptoms in terms of days, not hours and minutes, as with the therapy and accident data. For this study we needed response information in terms of hours for the first three days postexposure. (At least the Japanese data were not inconsistent with therapy and accident data: Oughterson et al. [1955] reported that in both cities about 70 percent of the exposed population vomited on the day of the bomb, and 11.5 percent vomited within the next 4 days.)

Despite those obvious limitations, we examined the Japanese data to see if they could make any contribution to our response model. This appendix describes how we evaluated the data and why we ultimately excluded them.

#### LEVELS OF RADIATION EXPOSURE

Figures A.1 and A.2 plot the doses to which victims were exposed at increasing distances from the blast center in Hiroshima and Nagasaki,

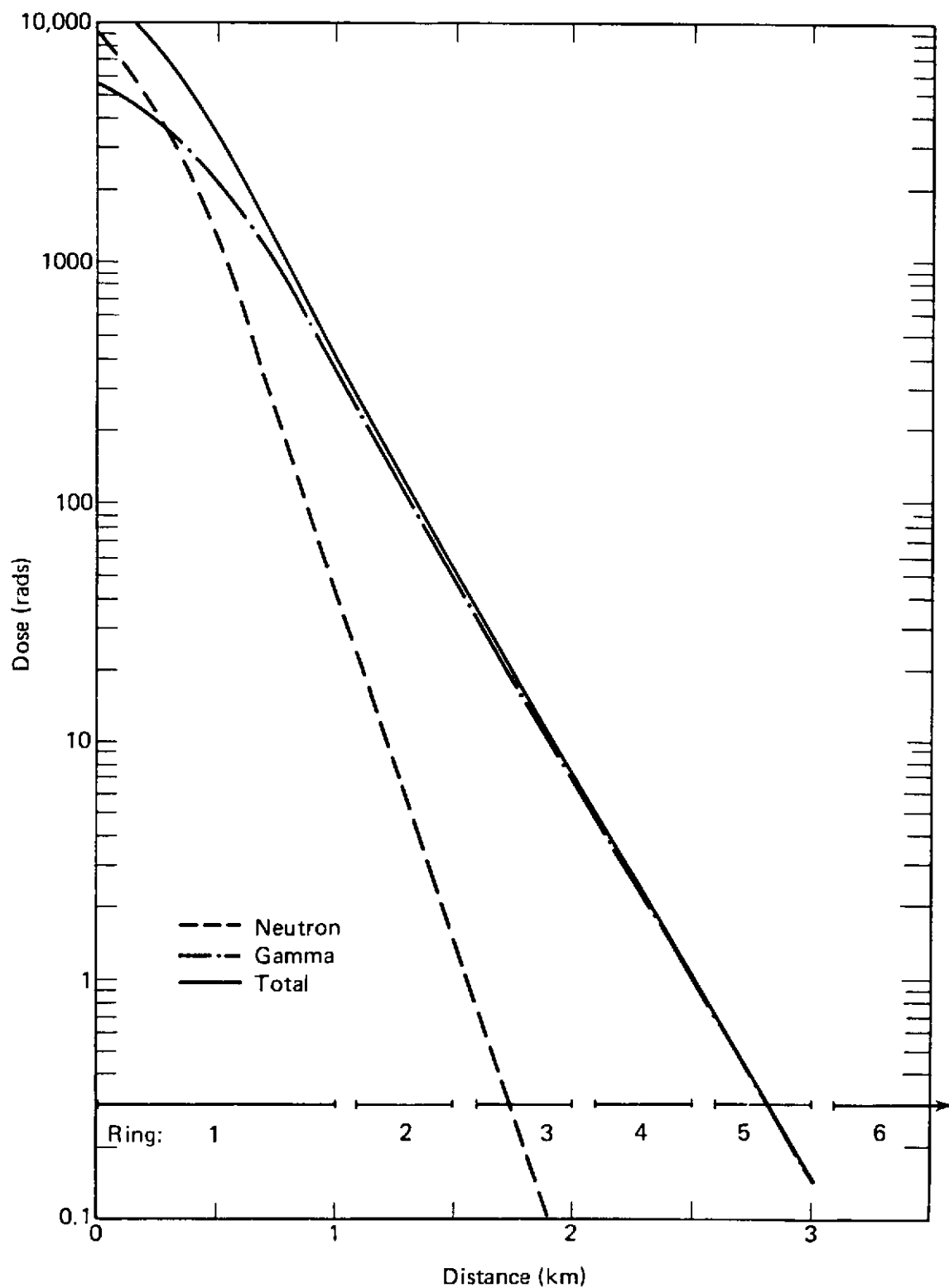


Figure A.1. Radiation dose from 15 kt Hiroshima atom bomb, by distance from blast center.

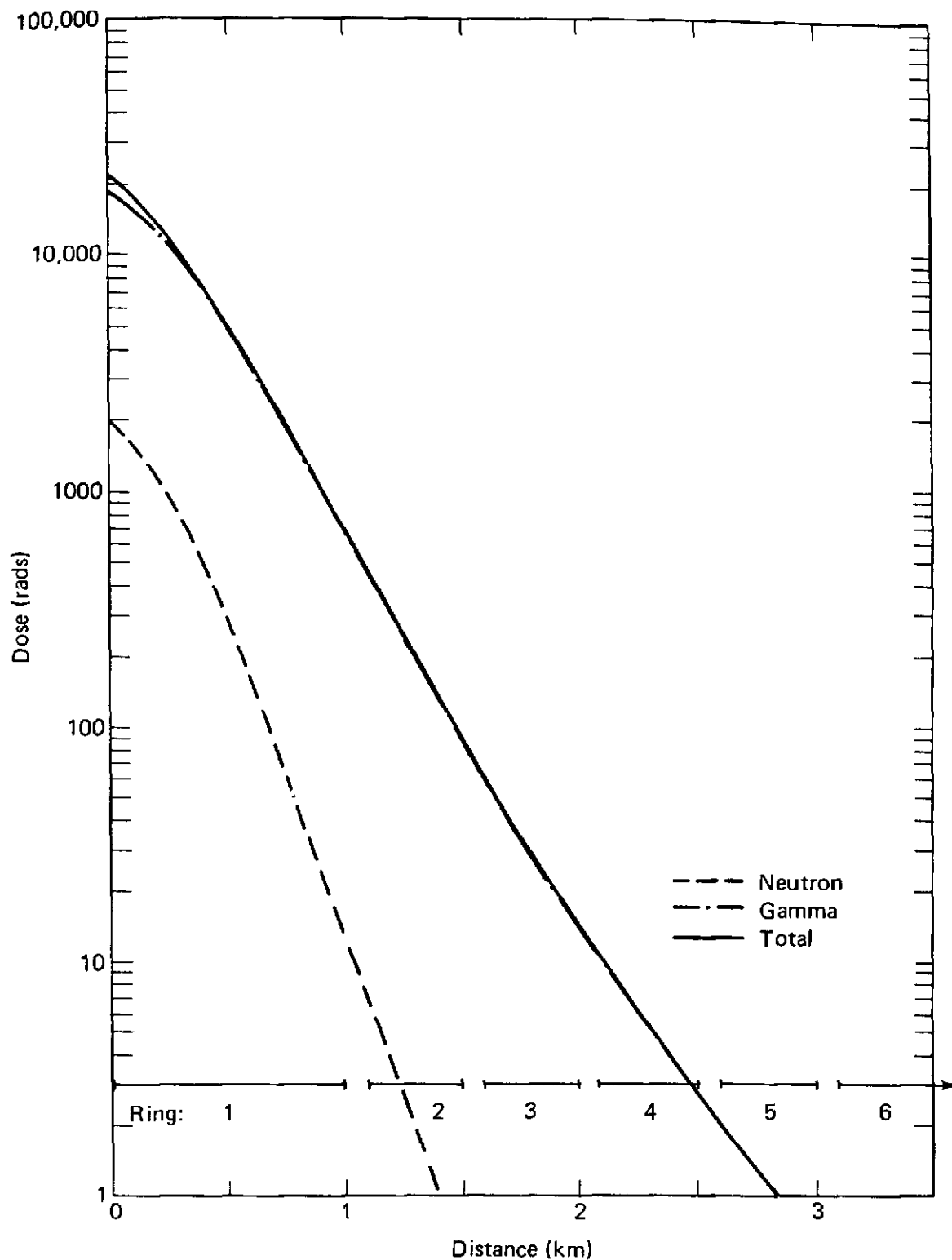


Figure A.2. Radiation dose from 22 kt Nagasaki atom bomb, by distance from blast center.

respectively. Each area is divided into rings bounded by concentric circles extending to about 3 km from the center. The graphs were drawn from revisions of the original dose estimates [Loewe and Mendelsohn, 1980; Mendelsohn, 1981]. The revised estimates begin at 600 m from ground zero; we extrapolated lesser values to the origin.

To relate dose with radiation sickness symptoms, we must first determine the average dose per ring. The following pages describe how we used the data in Figs. A.1 and A.2 to calculate those averages (the actual results are presented later in the appendix).

#### Average Dose per Ring--Hiroshima

For radial distances  $0 \leq r \leq 1$  km, either the neutron or gamma dose relationship  $D(r)$  can be approximated by the form

$$D(r) = \frac{A}{B + e^{kr}} \quad \text{rads} , \quad (\text{A.1})$$

where the constant values are as follows:

<u>Constant</u>	<u>Neutron</u>	<u>Gamma</u>
A	40,984 rads	19,100 rads
B	3.657	2.351
k	$6.78 \text{ km}^{-1}$	$3.93 \text{ km}^{-1}$

The average neutron or gamma dose for a radial distance  $0 \leq r \leq 1$   $\text{km}^{-1}$ , i.e., ring 1, is given by

$$\langle D \rangle_1 = \frac{1}{(R_1 - R_0)} \int_{R_0}^{R_1} \frac{A \, dr}{B + e^{kr}} = \frac{A}{B} \left\{ 1 + \frac{e^{kR_0} \left[ \frac{B + e^{kR_0}}{B + e^{kR_1}} \right]}{k(R_1 - R_0)} \right\} . \quad (\text{A.2})$$

Using the appropriate constant values, we obtained average neutron and gamma doses for ring 1, where  $R_0 = 0$  and  $R_1 = 1$  km, and added them to obtain the average total dose:  $\langle D \rangle_1 = \langle D \rangle_{1,\text{gamma}} + \langle D \rangle_{1,\text{neutron}}$ .

For radial distances  $1 \leq r \leq 3$  km, the total (i.e., neutron and gamma combined) dose relationship  $D(r)$  may be approximated by the form

$$D(r) \approx A_0 e^{-\alpha r},$$

where  $A_0 = 20,650$  rads,  
 $\alpha = 3.94 \text{ km}^{-1}$ .

Average total doses for  $r \geq 1$  km, i.e., rings 2 through 5, are given by

$$\begin{aligned} \langle D \rangle_{i+1} &= \frac{1}{R_{i+1} - R_i} \int_{R_i}^{R_{i+1}} A_0 e^{-\alpha r} dr \\ &= \frac{A_0}{\alpha(R_{i+1} - R_i)} \left[ \exp(-\alpha R_i) - \exp(-\alpha R_{i+1}) \right] \text{ rads}, \quad (\text{A.3}) \end{aligned}$$

where  $i$  = ring index,

$R_i, R_{i+1}$  = distances from blast center.

#### Average Dose per Ring--Nagasaki

For radial distances  $0 \leq r \leq 1$  km, the combined neutron and gamma dose relationship  $D(r)$  may be approximated by the form

$$D(r) = \frac{A}{B + e^{kr}} \text{ rads},$$

where the constant values are  $A = 41,893$  rads,  $B = 0.862$ , and  $k = 4.107 \text{ km}^{-1}$ .

Using Eq. (A.2) with those constants,  $R_0 = 0$ , and  $R_1 = 1$  km, we obtained the total average dose for ring 1.

For radial distances  $r \geq 1$  km, the total (combined neutron and gamma) dose relationship is given by

$$D(r) = A_i \exp (-\alpha_i r) \quad \text{rads} ,$$

where the following values obtain:

<u>Ring, i</u>	<u>Distance (km)</u>	<u><math>A_i</math> (rads)</u>	<u><math>\alpha_i</math> (<math>\text{km}^{-1}</math>)</u>
2	$1.5 \geq r \geq 1$	38,819	4.045
3	$2 \geq r \geq 1.5$	23,892	3.721
4	$2.5 \geq r \geq 2$	8,750	3.219
5	$3 \geq r \geq 2.5$	4,377	2.942
6	$3.5 \geq r \geq 3$	4,377	2.942

Average total doses for rings 2 through 6 are given by

$$\langle D \rangle_{i+1} = \frac{A_i}{\alpha_i (R_{i+1} - R_i)} \left[ \exp (-\alpha_i R_i) - \exp (-\alpha_i R_{i+1}) \right] ,$$

where  $i$  = ring index,

$R_i, R_{i+1}$  = distances from blast center

#### PRODROMAL SYMPTOMS

We used the per-ring average doses to classify by distance the incidence of nausea and vomiting as representative symptoms of prodromal radiation sickness. Table A.1 presents the results. The symptomatic data pertain to day 1 but were gathered by American physicians from survivors 20 days after the bombings [Oughterson et al., 1955]. The number of cases in each ring ensures that the responding percentages are reasonably precise. The pattern of vomiting here appears consistent with that observed among therapy patients and accident victims.

Figure A.3 displays the incidence of symptoms by dose, plotting the data in Table A.1 and adding data from therapy patients and accident



Table A.1. Nausea and vomiting among survivors of Hiroshima and Nagasaki bombings.

Ring	Distance from Blast Center (km)	Average Dose (rads)	Total Popu- lation	Vomiting		Nausea	
				Number Affected	Percent of Popu- lation	Number Affected	Percent of Popu- lation
<i>Hiroshima</i>							
1	0-1	4945	749	264	35.2	269	35.9
2	1.1-1.5	175	1125	290	25.8	321	28.5
3	1.6-2.0	25	1824	178	9.8	214	11.7
4	2.1-2.5	3.5	1450	106	7.3	148	10.8
5	2.6-3.0	.47	700	40	5.7	53	7.6
<i>Nagasaki</i>							
1	0-1	7190	789	213	27.0	223	28.5
2	1.1-1.5	292	1882	508	27.0	537	28.5
3	1.6-2.0	41	1034	163	15.8	164	15.9
4	2.1-2.5	7	672	62	9.2	73	10.9
5	2.6-3.0	1.5	644	44	6.8	54	8.4
6	3.1-4.0	.21	1141	55	4.8	58	5.1

victims for comparison [Langham (ed.), 1967]. The Langham data derive from probit analyses, assuming either a normal or log-normal distribution.\* At the low-dose end, Langham found a much better fit when a log-normal distribution was assumed; at the high-dose end the fit was better assuming a normal distribution. In Fig. A.3, accordingly, the Langham data are represented by two curves. The curve between 10 and 100 rads is based on a log-normal distribution, and the curve beginning at 40 rads is based on a normal distribution. The values at 70 rads in both curves are essentially equivalent.

The incidence of nausea and vomiting as a function of average dose was quite similar in the two Japanese cities. This suggests that despite the likely differences in radiation characteristics, relative biological effectiveness (RBE) in the two sites was similar for prodromal symptoms.

\* Lushbaugh et al. [1967] obtained similar data from probit analyses.

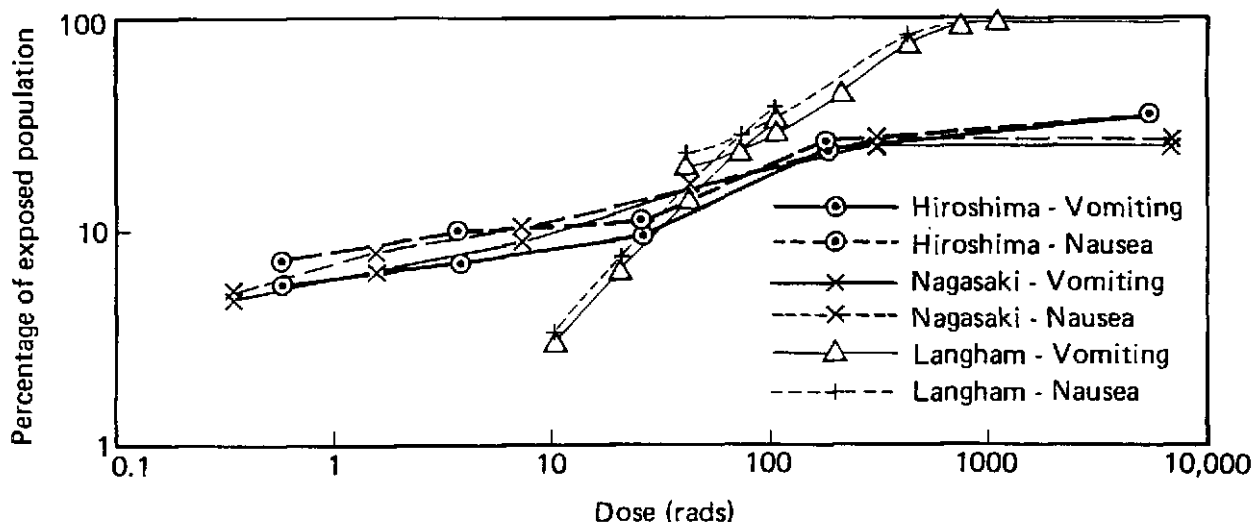


Figure A.3. Nausea and vomiting in atom bomb survivors (Hiroshima, Nagasaki) versus therapy patients and accident victims (Langham).

But the Japanese data differ markedly from the Langham data. At higher doses (more than 100 rads), the therapy and accident data suggest a more severe response than do the Japanese data; at lower doses the therapy and accident data suggest a lighter response. Since our investigation focuses on doses over 100 rads, how might we account for the differences in the two data sources at the higher doses?

One could hypothesize that the Japanese response appears lighter because most victims in rings 1 and 2 (blast center to 1.5 km) were exposed to the lowest doses recorded for the ring. Such an occurrence would lower the averages on which Fig. A.3 is based. However, Fig. A.1 suggests that for Hiroshima the lowest dose in ring 1 was ~400 rads, and that in ring 2 was ~50 rads. In Nagasaki, Fig. A.2, the corresponding lower limits were ~650 rads (ring 1) and ~90 rads (ring 2). Those doses are high enough to expect the Japanese responses to be much closer to those shown in the therapy and accident data.

Another possible explanation might be that many Japanese victims were shielded from the full effects of the free-in-air doses shown in Figs. A.1 and A.2. However, Oughterson et al. [1955] report that only 21 out of 1874 persons in Hiroshima, rings 1 and 2, were in bomb shelters or tunnels (in Nagasaki, 145 out of 2671). The rest in both cities were either outdoors or in Japanese types of structure, which afford relatively poor radiation shielding [Auxier, 1977].

It might also be postulated that those who gathered the Japanese data were dealing with a biased sample. Persons surviving after 20 days could represent the "healthier" or hyposensitive portion of the population; the majority might have been too sick to give an account of their illness and were overlooked in the study. The material reviewed offers no means of investigating that hypothesis.

The uncertainties surrounding the discrepancies manifested in Fig. A.3, plus more fundamental questions recently raised about the accuracy of the radiation levels particularly in Hiroshima [Marshall, 1981] persuaded us to exclude the Japanese atom bomb data from consideration in our Sec. 3 response model.



## Appendix B

### SIDE EFFECTS OF TOTAL-BODY IRRADIATION IN THERAPY PATIENTS

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Physicians and medical researchers have been less interested in the side effects of therapeutic total-body irradiation (TBI) than in its effects on the disease itself. As a result, there is a dearth of published data on the manifestations and interpretation of acute radiotoxicity. To improve our understanding of symptomatic responses for the present investigation, I have gathered what is known about the subject from published sources and from my own and colleagues' observations.

In the past decade at least 1500 patients have been treated with TBI, mainly for leukemia but also for aplastic anemia and other diseases. A substantial number of patients have been treated with half-body irradiation, where either one-half of the body is irradiated or both halves are irradiated sequentially, with an interval of 6 to 8 weeks between treatments to allow for repopulation of irradiated bone marrow from the other half of the body. Some patients with chronic lymphatic leukemia or lymphoma have been treated with multiple small dose increments (e.g., 10 rads) adding to low total doses (e.g., 120 to 200 rads). Finally, a group of patients with mycosis fungoides have been treated over their total skin surface using electrons that penetrate only about 1 cm.

#### IRRADIATION METHODS AND DOSIMETRY

The dosimetry has not always been optimal, but most specified doses have probably been accurate to  $\pm 10$  percent. The doses have usually been specified at mid-body; therefore, near the body surface and in thinner regions such as the head, neck, and limbs doses have been higher by up to 15 percent. The radiation has always been in the million-electron-volt range, usually from a cobalt 60 source but sometimes using linear accelerators producing up to 25 MeV.

The radiation methods can be grouped as follows:

1. TBI, single exposure, low dose rate: 4 to 12 rads/min, total dose, 800 to 1200 rads.
2. TBI, single exposure, high dose rate: 20 to 25 rads/min, total dose, 750 rads.
3. TBI, up to 6 or 8 exposures, high dose rate: 200 rads/day, several hours apart, total dose, 1200 to 1600 rads.
4. TBI, multiple small exposures, high dose rate: 10 rad exposure, total dose, 120 to 200 rads.
5. TBI of skin using 2.5 MeV electrons: fractional dose,  $\leq 200$  rads, total dose, 800 to 4000 rads.
6. Half-body radiation or sequential half-body radiation at high dose rate using total doses of 600 to 1000 rads.

The remainder of this appendix focuses on responses to methods 1 through 3, which most closely resemble high-dose-rate single exposures of 750 to 1000 rads.

#### FACTORS MODIFYING IRRADIATION RESPONSE (750 to 1000 RAD DOSE EQUIVALENTS)

All patients had a life-threatening disease although some were in reasonably good condition; many were young.

Patients were not stressed. Most were treated with extreme care, and many were placed in "life islands" where conditions were maximally favorable to asepsis. To counter the ill effects of radiation exposure, all patients were given sedatives, antiemetics, steroids, and intravenous fluids before their treatments.

Before undergoing TBI, most patients had received large doses of chemotherapy. That treatment could have contributed to the severity of the postirradiation skin and mucosal reactions and perhaps to sequelae in other organs. The depletion of normal bone marrow cells resulting from chemotherapy probably did not significantly alter patients' initial radiation responses such as nausea and vomiting. (Longer-term hemopoietic effects of radiation exposure would have been altered,

however, because all patients undergoing TBI received bone marrow grafts after irradiation.)

#### ACUTE SEQUELAE (750 TO 1000 RAD DOSE EQUIVALENTS)

Shortly after exposure, most patients experienced *nausea, emesis, chills, and fever*. Those symptoms usually subsided within about 10 hr and disappeared within 24 hr except for nausea and anorexia, which could persist for days. Emesis was aggravated by movement and often occurred with little warning.

In the first few hours after exposure, some patients experienced *decreased blood pressure and increased pulse rate* due to circulatory hypovolemia. There were reports of acute myocardial insufficiency and death in patients with a history of myocardial disease.

A painful mumps-like *swelling of the parotid gland* developed within a few hours of exposure. The pain usually subsided within 2 days; the swelling sometimes persisted for several days. Xerostomia (dry mouth) sometimes lasted a week or more. During that time the saliva was reduced in volume, was thicker, and felt ropey. A metallic taste could persist as long as the mouth remained dry. Reduced salivary secretion added to patients' disinterest in food.

About 10 percent of the patients developed *diarrhea* soon after irradiation. More developed diarrhea 1 to 7 days after exposure.

The *oropharyngeal mucosae* became reddened and sore 1 to 3 days after exposure and subsequently ulcerated. The condition took about 3 weeks to disappear. About 75 percent of the patients developed *oral infections*, owing not only to the ulcerated mucosae but also to leukocytopenia and immunosuppression. These infections became apparent as soon as 3 days after irradiation. The most common were fungal (thrush), but bacterial and herpes infections were also seen.

A generalized *erythema* appeared as soon as 1 day after irradiation though usually later. It persisted for as long as 2 weeks and was sometimes associated with perineal irritation and itchiness. Beginning 7 to 10 days after exposure there was a temporary incomplete *loss of hair*. Sweating appeared to decrease in some patients, but that phenomenon has not been adequately investigated.

*Bone marrow suppression* was indicated by increased susceptibility to infections and bleeding (e.g., of the gums) several days after exposure. If the patient had a preexisting infection, however, TBI was usually fatal, sometimes during the first postexposure week. Bone marrow grafts did not mitigate that result.

#### RESPONSE TO HIGHER SKIN DOSES

When doses of electrons equivalent to a single exposure of 1000 to 2000 rads were given to the skin, the incidence and severity of responses described above increased. The most important seemed to be decreased sweating associated with a generalized burning sensation and a low tolerance to exercise or heat with consequent high risk of hyperthermia. That phenomenon has been little investigated in patients treated with electrons that penetrated about 1 cm below the skin. In X- or gamma-ray treatments, the energy of the beams was high enough to "spare" the skin. The electron treatments, with doses that produced only partial epilation and decreased sweating, also resulted in a loss of fingernails; how soon after exposure was not indicated. (In current skin treatments with electrons, fingernails are protected by lead shields.)

#### PROBLEMS IN ASSESSING SIDE EFFECTS

##### Little Data on Effects of TBI at Less Than 750 Rads

Very few patients (e.g., about 20) received 300 rad doses of TBI; data on the side effects they experienced have not been published. Continuing attempts to optimize and individualize dose regimens may permit a better assessment of dose-response relationships.

##### Multiple Variables

The premedication and management of patients receiving TBI is improving. Acute side effects have been alleviated by premedication with antiemetics, steroids, and intravenous fluids. Infections have been reduced by preradiation decontamination and by not treating patients



having evidence of infection. It would be useful to try to reconstruct what the results of treatment would have been without such sophisticated measures for reducing morbidity.

#### Importance of Inhibition of Sweating Unknown

Inhibition of sweating is not a problem in usual clinical radiotherapy because only small surface areas are irradiated. It could be lethal if large single doses are delivered from sources that do not spare the skin. Sweating was studied in patients receiving a series of small doses over a 6 week period. It is difficult to estimate the single-dose equivalent from the published data, but it is less than 2000 rads and perhaps about 1500 rads.

#### PROSPECTIVE STUDIES

In the effort to pursue a careful, comprehensive, and quantitative examination of TBI effects on normal tissue, we need to know more about postexposure fatigability and sweating patterns. Only one report has mentioned fatigability. Twenty-seven patients were treated with only 10 rads per day, three or five times per week, for total doses of 120 to 200 rads. Even at such low doses, two patients complained early of fatigability, and "most" complained of it 2 weeks to 4 months after the completion of treatment. Evidence of fatigability is not usually sought in patients treated with high doses of TBI because they are sicker and have more restricted mobility than patients receiving small fractional doses. But fatigability would be a significant factor in considering radiation effects in otherwise healthy adults. Sweating patterns could be investigated in patients receiving high doses of radiation to the skin, as for skin or breast cancer.



## Appendix C

### FORMULAS UNDERLYING THE RESPONSE MODEL

At the end of Sec. 3, we set forth the basic concepts of a model linking individual and population responses in the initial period as a function of dose. The model was illustrated in Figs. 15 and 16. This appendix presents algebraic formulas that explain how values for the curves in Figs. 15 and 16 could be derived. If these functional relationships can be established, it will be possible to add the time dimension, now omitted, to Figs. 15 and 16.

We assume that the following are known:

- $x_1$ , percentage of hypersensitives in population (~15 to 25)
- $x_2$ , percentage of normosensitives in population (~50 to 70)
- $x_3$ , percentage of hyposensitives in population (~15 to 25)
- $D_1$ , threshold response dose for hypersensitives (100 rads)
- $D_2$ , threshold response dose for normosensitives (150 rads)
- $D_3$ , threshold response dose for hyposensitives (200 rads).

We also presume the following:

- $y_a$ , maximum incapacitation for unaffected (10 percent)
- $y_b$ , maximum incapacitation for mildly affected (30 percent)
- $y_c$ , maximum incapacitation for moderately affected (60 percent)
- $y_d$ , maximum incapacitation for severely affected (100 percent)
- $D'_1$ , dose producing maximum incapacitation in hypersensitives  
(few hundred rads)
- $D'_2$ , dose producing maximum incapacitation in normosensitives  
(several hundred rads)
- $D'_3$ , dose producing maximum incapacitation in hyposensitives  
(few thousand rads).

We define the portion of the population by symptom severity as

$f_{un}$ , percentage unaffected  
 $f_{mild}$ , percentage mildly affected  
 $f_{mod}$ , percentage moderately affected  
 $f_{sev}$ , percentage severely affected.

We require that

$$f_{un} + f_{mild} + f_{mod} + f_{sev} = x_1 + x_2 + x_3 = 100 . \quad (C.1)$$

The two response-group classifications can be linked by considering an arbitrary dose designated D. Thus, the percentage of hypersensitives that are severely affected is

$$f_{1,sev} = \left( \frac{y_{1,sev} - y_c}{y_d - y_c} \right) x_1 , \quad y_c \leq y_{1,sev} \leq y_d . \quad (C.2)$$

Since at D the cumulative response function  $y_{1,sev}$  exists somewhere between the upper limits of the moderately and severely affected boundaries, for simplicity we assign all other hypersensitives to the next lower severity category. The percentage of hypersensitives that are moderately affected is then

$$f_{1,mod} = \left( 1 - \frac{y_{1,sev} - y_c}{y_d - y_c} \right) x_1 . \quad (C.3)$$

Similarly, the percentage of normosensitives that are moderately affected is

$$f_{2,mod} = \left( \frac{y_{2,mod} - y_b}{y_c - y_b} \right) x_2 , \quad y_b \leq y_{2,mod} \leq y_c , \quad (C.4)$$

and the percentage that are mildly affected is

$$f_{2,mild} = \left( 1 - \frac{y_{2,mod} - y_b}{y_c - y_b} \right) x_2 . \quad (C.5)$$

The percentage of hyposensitives that are mildly affected is

$$f_{3,mild} = \left( \frac{y_{3,mod} - y_a}{y_b - y_a} \right) x_3 , \quad y_a \leq y_{3,mod} \leq y_b . \quad (C.6)$$

Then at dose D the population response distribution (Fig. 16) is

$$\text{Severely affected: } f_{sev} = f_{1,sev} , \quad (C.7)$$

$$\text{Moderately affected: } f_{mod} = f_{1,mod} + f_{2,mod} , \quad (C.8)$$

$$\text{Mildly affected: } f_{mild} = f_{2,mild} + f_{3,mild} , \quad (C.9)$$

$$\text{Unaffected: } f_{un} = 100 - (f_{sev} + f_{mod} + f_{mild}) . \quad (C.10)$$

Some boundary relationships can now be readily established. In addition to requiring Eq. (C.1) above, we set the boundary conditions listed below. Numbers 1 and 2 are external, 3 through 6 are internal.

$$1. \text{ At } D_1: f_{un} = 100, f_{mild} = f_{mod} = f_{sev} = 0 . \quad (C.11)$$

$$2. \text{ At } D_3: f_{sev} = x_1 + x_2 + x_3 = 100 , \quad (C.12)$$

$$f_{un} = f_{mild} = f_{mod} = 0 . \quad (C.13)$$

$$3. \text{ For } D \geq D'_2: f_{un} = f_{mild} = 0, \quad (C.14)$$

$$f_{sev} = x_1 + x_2 + f_{3,sev}, \quad (C.15)$$

$$f_{mod} = 100 - f_{sev}, \quad (C.16)$$

$$\text{where } f_{3,sev} = \left( \frac{y_{3,sev} - y_c}{y_d - y_c} \right) x_3,$$

$$y_c \leq y_{3,sev} \leq y_d. \quad (C.17)$$

$$4. \text{ At } D'_1: f_{sev} = x_1 + f_{2,sev}, \quad (C.18)$$

$$f_{mod} = f_{2,mod} + f_{3,mod}, \quad (C.19)$$

$$f_{mild} = f_{3,mild}, \quad (C.20)$$

$$f_{un} = 0, \quad (C.21)$$

$$\text{where } f_{2,sev} = \left( \frac{y_{2,sev} - y_c}{y_d - y_c} \right) x_2,$$

$$y_c \leq y_{2,sev} \leq y_d, \quad (C.22)$$

$$f_{2,mod} = \left( 1 - \frac{y_{2,sev} - y_c}{y_d - y_c} \right) x_2, \quad (C.23)$$

$$f_{3,mod} = \left( \frac{y_{3,mod} - y_b}{y_c - y_b} \right) x_3,$$

$$y_b \leq y_{3,mod} \leq y_c, \quad (C.24)$$

$$f_{3,mild} = \left( 1 - \frac{y_{3,mod} - y_b}{y_c - y_b} \right) x_3. \quad (C.25)$$

$$5. \text{ At } D_2: f_{\text{sev}} = f_{\text{mod}} = 0, \quad (\text{C.26})$$

$$f_{\text{mild}} = f_{1,\text{mild}}, \quad (\text{C.27})$$

$$f_{\text{un}} = 100 - (f_{\text{mild}} + f_{\text{mod}} + f_{\text{sev}}), \quad (\text{C.28})$$

$$\text{where } f_{1,\text{mild}} = \left( \frac{y_{1,\text{mild}} - y_a}{y_b - y_a} \right) x_1$$

$$y_a \leq y_{1,\text{mild}} \leq y_b. \quad (\text{C.29})$$

$$6. \text{ At } D_3: f_{\text{mild}} = f_{1,\text{mild}}, \quad (\text{C.30})$$

$$f_{\text{sev}} = f_{\text{mod}} = 0, \quad (\text{C.31})$$

$$f_{\text{un}} = 100 - (f_{\text{mild}} + f_{\text{mod}} + f_{\text{sev}}), \quad (\text{C.32})$$

$$\text{where } f_{1,\text{mild}} = \left( \frac{y_{1,\text{mild}} - y_a}{y_b - y_a} \right) x_1,$$

$$y_a \leq y_{1,\text{mild}} \leq y_b. \quad (\text{C.33})$$





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